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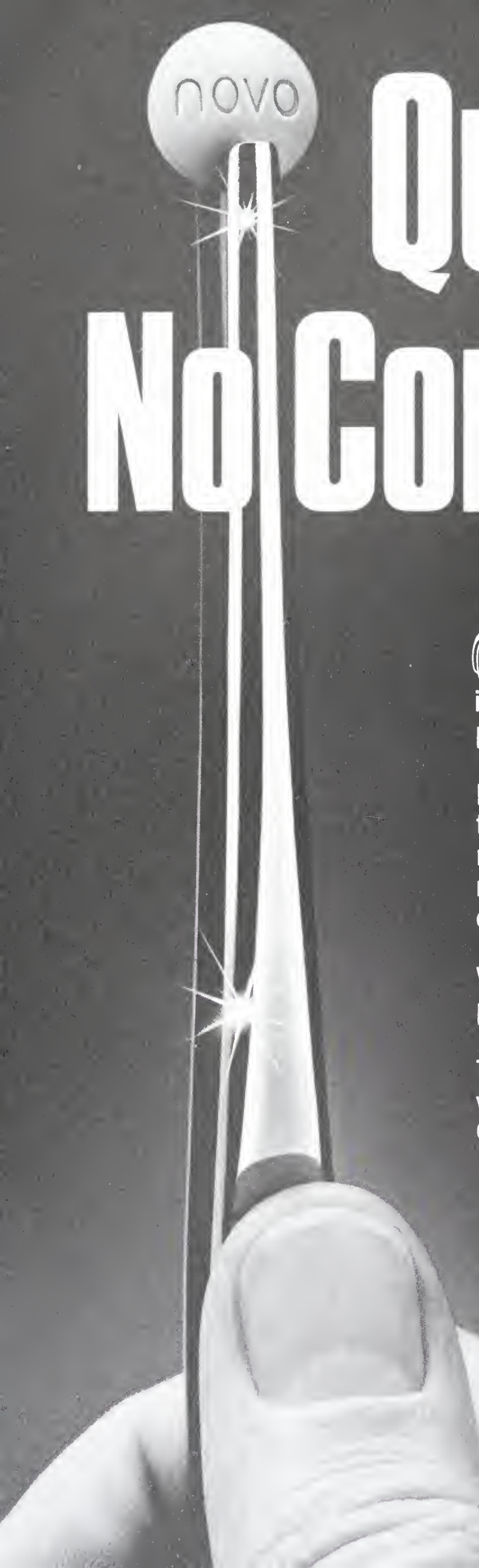

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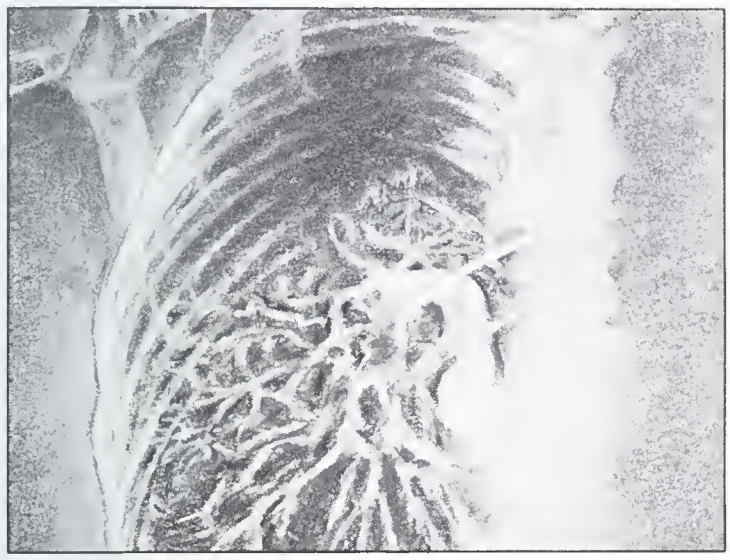

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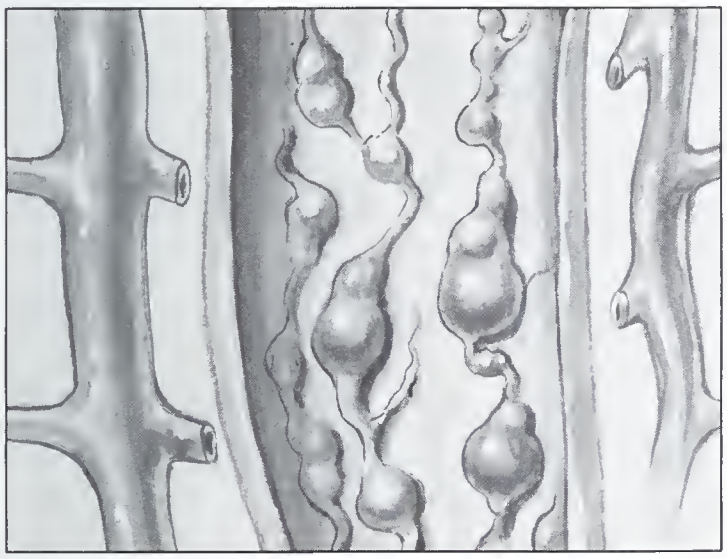

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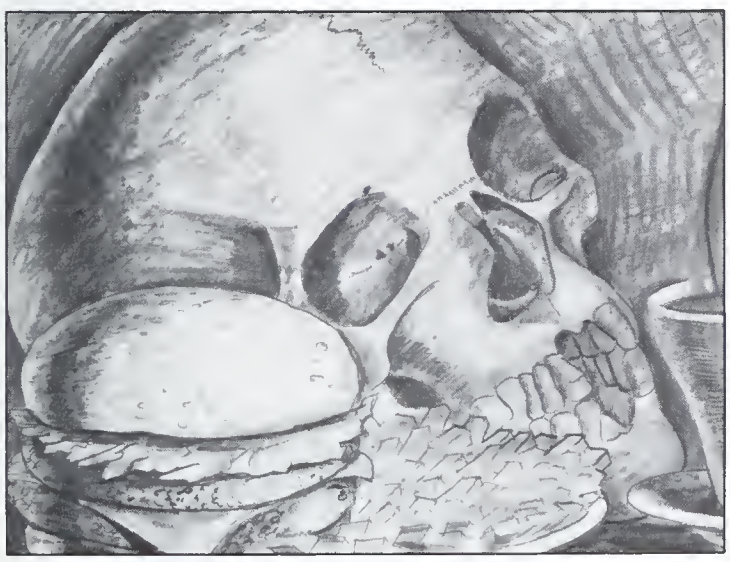

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Front cover illustration by Beverly Nash, Department of Biomedical Communications, Faculty of Medicine, University of Toronto.

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Editorial

Dear Readers,

It is fitting that the contents of this year's third and final issue reflect a predominence of articles clustered around the subject of cancer. This underscores how, despite the preponderance of oncology research, cancer and the spectrum of diseases it encompasses remains an awesome presence in our personal and professional lives. The authors presented here approach this broad field from a host of perspectives, covering nutritional, genetic, and surgical aspects of cancer and its management. In addition, this issue features a report on the recently held National Forum on Breast Cancer discussing, among other things, broader epidemiologic and social aspects of this disease. The report includes an interview with Dr. Roy Clark, radiation oncologist and Chair of the Forum's Scientific Committee.

This issue contains another interview of note: Dr. Robert Salter, University Professor and Chief of Surgery at Toronto's Hospital for Sick Children, shares his views on life as a clinician-scientist and his advice to those currently in medical training. This unique discussion with the world-renowned orthopaedic surgeon is found in the News & Views section.

Finally, our feature article presents a rare case report of an extrapulmonary arteriovenous fistula. The accompanying discussion provides an excellent illustration and review of the literature regarding this unusual entity.

It is traditional in the final issue of the year to acknowledge the efforts and contributions of the Journal staff. We would like to extend our deepest appreciation to our treasurer Tamarah Kagan and our News & Views editor D'Arcy Little for their tremendous assistance throughout the year. We are also grateful to our art director Loretta De Groot and the Biomedical Communications students, and to book reviews editor Amy Freedman, for their work. Finally, we extend our thanks to our associate editors David Gladstone, Angela Luong, and Michael Schweitzer and to the many members of our editorial board. We wish the new incoming editors the best of luck.

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Case Report of a Patient with an Extrapulmonary Arteriovenous Fistula

Anthony C. Luke (9T5), Richard A. Malthaner, M.D., F.R.C.S.(C), B.Sc.*
and Timothy L. Winton, M.D., F.R.C.S.(C), B.Sc., M.Sc.**

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Abstract

Pulmonary arteriovenous fistula is a rare condition representing a direct communication between the pulmonary artery and vein. We report a case of a patient with an extrapulmonary arteriovenous fistula between the right main pulmonary artery and the left atrium. The patient demonstrated a classic presentation of symptoms and was treated by surgical ligation of the fistula. Our patient's lesion, however, was atypical since it was extrapulmonary rather than intraparenchymal. We review the literature, discussing the approach to a patient with pulmonary arteriovenous fistula. The complete work-up involves chest imaging, arterial blood gas measurement, contrast echocardiogram, and angiography which is the gold standard. Treatment options consist of surgical ligation, surgical resection, or therapeutic embolization.

Introduction

Pulmonary arteriovenous fistulas are rare congenital malformations that represent direct communications between the pulmonary artery and vein without an intervening capillary bed[1]. A right-to-left shunt is established and symptoms develop when a sufficient amount of deoxygenated blood directly enters the systemic circulation. These malformations usually occur among the peripheral intrapulmonary vessels, supported by lung parenchyma. We report a case of a patient with an extrapulmonary arteriovenous fistula and discuss the current management of this unusual condition.

Case Report

Figure 1: Chest roentgenogram of our patient with PAVF showing slight right hilar prominence (arrow) on the PA view.

A 33 year-old woman with a long-standing history of shortness of breath on exertion presented with increased dyspnea at rest and left-sided pleuritic chest pain. She was a 6 pack-year smoker with no previous history of asthma, lower respiratory tract infection, tuberculosis, or deep venous thrombosis. She stated that she suffered from chronic orthostatic hypotension. She reported no cough, sputum, or hemoptysis.

Physical examination revealed central cyanosis and clubbing, but no telangiectasia. The patient had a normal systemic blood pressure and no clinical signs of right or left-sided heart failure. The chest was clear to auscultation. Arterial blood gases showed a PaO_2 of 50 mmHg on room air which improved minimally to a PaO_2 of 69 mmHg on 100% O_2. Her $PaCO_2$ was 31 mmHg and her calculated alveolar-arterial O_2 gradient ($AaDO_2$) was 61 mmHg. The patient's hemoglobin was 173 g/L and her leukocyte count was 7.7 x109/L. Her prothrombin time was 12.3 s, and the activated partial thromboplastin time was 28.9 s. A chest roentgenogram showed a slight right hilar prominence (Figure 1). The lateral radiograph displayed a 1.6 cm nodular opacity posterior to the hilum.

The patient was initially investigated to rule out pulmonary embolus as the cause for the chest pain and refractory hypoxemia. A ventilation-perfusion lung scan indicated a low probability of thromboembolic disease and a venogram demonstrated no DVT. An echocardiogram showed no changes in right-sided function or pressures and no evidence of an intracardiac shunt. An angiogram was done, revealing an arteriovenous malformation measuring 1.7 to 1.9 cm in diameter. This originated from the right main pulmonary artery just proximal to the right lower lobe branch and communicated directly with the left atrium (Figure 2).

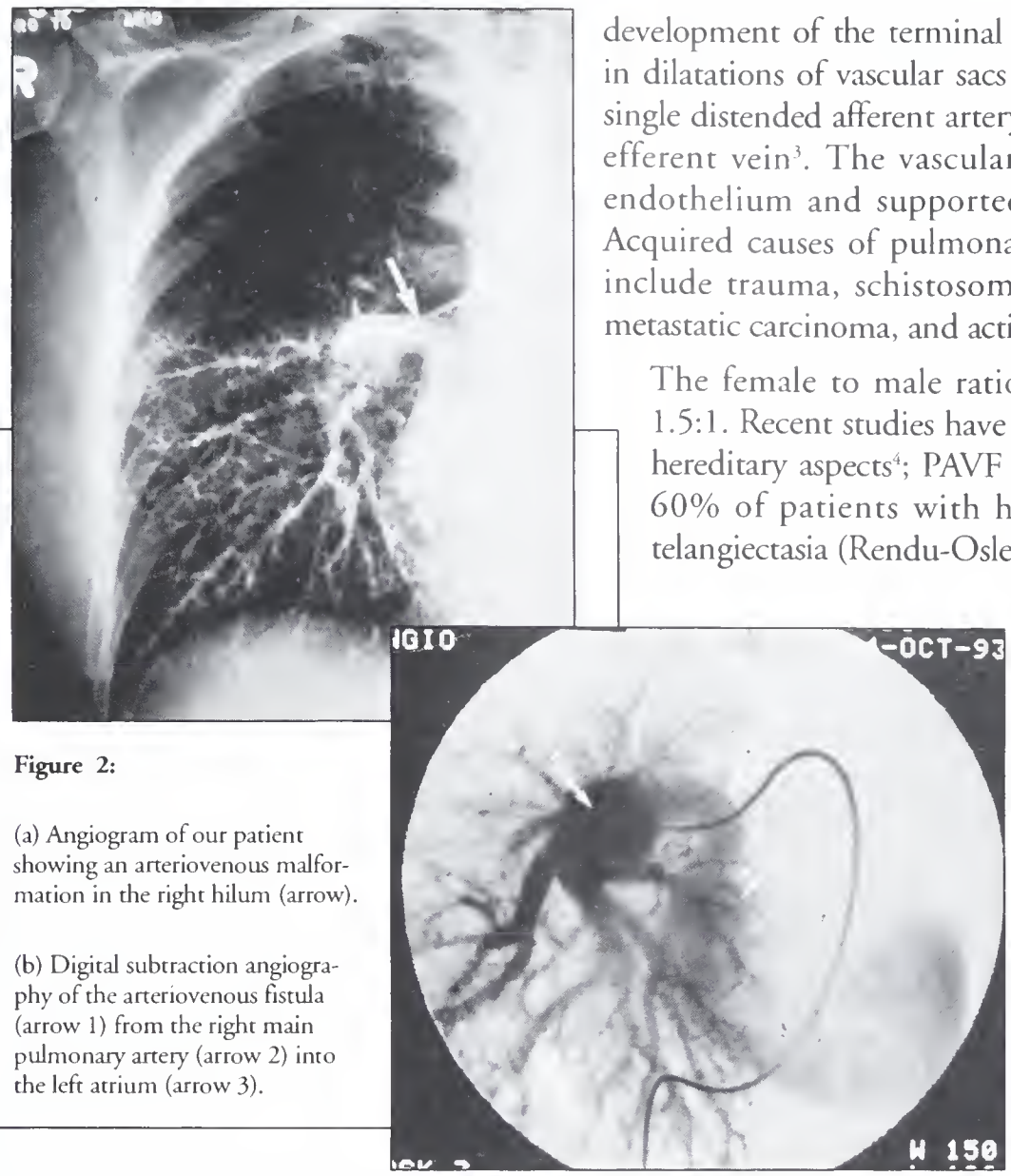

Figure 2:

(a) Angiogram of our patient showing an arteriovenous malformation in the right hilum (arrow).

(b) Digital subtraction angiography of the arteriovenous fistula (arrow 1) from the right main pulmonary artery (arrow 2) into the left atrium (arrow 3).

At thoracotomy, a large extrapulmonary arteriovenous fistula (PAVF) was found arising from the right pulmonary artery and coursing directly into the left atrium flush with the pericardium (Figure 3). After surgical ligation, the intra-operative PaO_2 on 100% O_2 with unilateral left lung ventilation immediately improved from 74 to 158 mmHg. The initial PaO_2 with bilateral ventilation was 179 mmHg and improved to 506 mmHg post ligation of the fistula. Post-operative recovery was prolonged due to a persistent parenchymal air leak with subsequent formation of a small loculated empyema necessitating surgical drainage. The patient has now recovered and is doing well.

Discussion

Pulmonary arteriovenous malformation (PAVM), pulmonary arteriovenous aneurysm (PAVA), and pulmonary arteriovenous fistula (PAVF) are terms used to describe an abnormal direct communication between the pulmonary artery and the vein without an intervening capillary bed. PAVF is an uncommon abnormality and was first reported in 1897[2]. It may be intra- or extraparenchymal, the former being much more common. While the majority are congenital in origin, they may be acquired. The most popular theory for congenital formation of PAVF is abnormal development of the terminal capillary loops, resulting in dilatations of vascular sacs which are supplied by a single distended afferent artery and drained by a single efferent vein[3]. The vascular channels are lined by endothelium and supported by connective tissue. Acquired causes of pulmonary arteriovenous fistula include trauma, schistosomiasis, hepatic cirrhosis, metastatic carcinoma, and actinomycosis[3].

The female to male ratio has been found to be 1.5:1. Recent studies have shown that there may be hereditary aspects[4]; PAVF has been associated with 60% of patients with hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease)[3].

The pulmonary fistulas are multiple in 33 to 50% of patients and are bilateral in 8 to 20%[3]. They vary in size from microscopic to 4 cm in diameter and are usually found close to the pleura. They are more often found in the lower lobes. Fistulas originate most commonly from the pulmonary artery

Figure 3: Intra-operative photograph of our patient with PAVF (arrows 1) showing the lesion through a right thoracotomy. The posterior chest wall (2) is on the left of the photograph while the lower lobe of the lung (3) is being retracted inferiorly. The PAVF (arrows 1) is travelling posteriorly from the right main pulmonary artery (arrow 4) and directly communicates with the left atrium (arrow 5).

(96%) or a systemic artery such as the bronchial arteries, the intercostal arteries, or the aorta. With a sufficiently large fistula (greater than 2 cm), a significant right-to-left shunt develops. When greater than 20% of pulmonary blood flow is shunted, the arterial blood may become substantially desaturated, producing symptoms[3].

Clinical Findings

The triad of dyspnea on exertion, cyanosis, and clubbing is classic for PAVF and was present in our patient. As well, patients may present with hemoptysis and chest pain. Patients with Rendu-Osler-Weber disease may also have telangiectasia, epistaxis, hematuria, and melena. In addition, associated hypoxia and secondary polycythemia may cause CNS abnormalities such as headache, vertigo, numbness, paresis, syncope, confusion, and dysphagia[3]. Our patient's history of orthostatic hypotension may have been due to shunting and hypoxia. Asymptomatic patients present with abnormal chest X-rays in approximately 98% of cases[5].

Findings on physical examination may include cyanosis, clubbing, an increased second heart sound, a pulmonary bruit, telangiectasia, and a pansystolic murmur with a thrill that decreases with the Valsalva manoeuvre[3] and increases with inspiration (Muller's manoeuvre).

Approach to Patient Management

Initial work-up should include a complete blood count, arterial blood gas measurements, chest roentgenogram, and echocardiogram. Bloodwork may reveal polycythemia with increased reticulocytes, as well as leukocytosis. The chest roentgenogram usually demonstrates a peripheral circumscribed noncalcified lesion, similar to a coin lesion, connected by blood vessels to the hilum (Figure 1). The lesion is better defined by CT scan. Contrast echocardiography helps localize small right-to-left shunts to the cardiac or pulmonary level and to assess residual shunting after surgery. Angiography, however, is the gold standard. It must be used to determine the size, number, and location of the fistulas before any definitive treatment is undertaken[4]. Less commonly used is radionuclide ventriculography using technetium 99m-labelled red blood cells, which enables the cardiac ejection fraction to be calculated and estimates the magnitude of the shunt. Perfusion lung scintigraphy uses radioactive albumin which collects in pulmonary capillary beds and is absent in the systemic circulation unless a fistula is present, in which case bypassed areas of the lung appear as "cold" areas[3]. Any patient suspected of hereditary hemorrhagic telangiectasia should be screened with chest radiography, arterial blood gases, and possibly CT scan. If findings are abnormal, an angiogram is indicated.

Complications of PAVF include thrombus formation in the fistula, bacterial endarteritis within the fistula, sudden massive hemoptysis or hemothorax, and paradoxical embolism leading to ischemic stroke or cerebral or peripheral abscess formation[6]. White and colleagues report an 18% incidence of stroke and a 37% incidence of TIAs[7]. Sisel et al. report the incidence of neurological complications due to hypoxia and polycythemia to be around 33%[8]. Schumacker and Waldhausen report that vascular complications occurred in 20-30% of patients with hereditary hemorrhagic telangiectasia [9].

Treatment of intraparenchymal PAVF is determined by assessing the patient's adaptation to the disease, number and size of lesions, and ability of the patient to tolerate surgery. The treatment of a solitary PAVF is surgical dissection and local excision of the aneurysmal sac while preserving lung parenchymal tissue. Segmental resection with removal of lung parenchyma is performed for deep lesions and lobectomy is considered for a conglomerate arteriovenous aneurysm, which involves the lobe in a multicentric fashion[4]. Studies by Dines in 1974 report no mortality and negligible morbidity for patients undergoing surgical resection (n=33) compared to patients receiving no treatment (n=27), who experienced 26% morbidity and 11% mortality[10]. Single extra-pulmonary PAVF easily lend themselves to surgical ligation.

Another option for treatment involves embolization of the pulmonary artery proximal to the malformations with nonabsorbable steel coils, silicone balloons, nylon brushes or other materials[11]. Embolization is useful in multiple, recurrent, or bilateral PAVF, avoiding repeated surgery, general anesthesia, and loss of pulmonary parenchyma. Complications of embolization include paradoxical embolus and pulmonary infarction should the coil be placed too distally or proximally, respectively[5]. Regardless, definitive treatment is recommended even in asymptomatic patients due to the complications associated with PAVF.

Our patient had a classical presentation of PAVF. Her chest X-ray showed a nodule and the fistula was confirmed on angiography. However, her lesion was unusual because she presented with an extrapulmonary arteriovenous fistula. A literature review, including major studies and collective reviews on PAVF, made no mention of the type of extrapulmonary AVF we have described. Our patient's fistula arose from the posterior aspect of the right main pulmonary artery proximal to the takeoff of the lower lobe superior segmental pulmonary artery and coursed posterior to the superior segmental bronchus. It then entered the left atrium at the junction with the pericardium and the inferior pulmonary vein. Surgical ligation was performed because the lesion was large and singular and radiological embolization would present the risk of an embolus to the heart and the systemic circulation. The intra-operative PaO_2 with one lung ventilated was almost the same as with both lungs, indicating that a significant shunt was present. The patient's PaO_2 and exercise tolerance improved dramatically following the operation.

Summary

A pulmonary arteriovenous fistula should be considered in the differential diagnosis of a patient with dyspnea on exertion, cyanosis, and clubbing, especially if hereditary hemorrhagic telangiectasia is present. Due to the risk of complications, these patients should be screened and treated. Complete work-up includes chest radiographic imaging, arterial blood gas measurements, contrast echocardiography, and angiography. Treatment consists of surgical excision for singular or localized lesions, while therapeutic embolization is indicated for multiple fistulas. These therapies have been proven to reduce morbidity and mortality in patients with pulmonary arteriovenous fistulas.

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AWARDS

The R.I. Harris Undergraduate Award in Orthopaedics has been awarded to Michael Gilbart, 9T5 for his article "Chronic Pain Following Ankle Sprains: Aetiology, Classification and Management."

The Gladstone Neuroscience Award has been awarded to Ophyr Mourad, 9T6 for his article "The Mystery of Rett Syndrome: A Review of the Current Literature."

The UTMJ Prize for Literary Excellence has been awarded to Douglas Lee, 9T4 for his article "Perspectives on Interventional Cardiology and Advances in Invasive Methods."

ERRATA

In the previous issue, an X-ray in the Quick Diagnosis article (p.62, Figure 2) was printed upside down.

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Non-Surgical Management of an Acute Esophageal Varix Hemorrhage

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Abstract

In North America, alcoholism is the leading cause of cirrhosis and thus the leading cause of portal hypertension and esophageal varices. Most patients bleed from varices at the gastro-esophageal junction. A 50% mortality rate is associated with the first bleed and so appropriate treatment is imperative. The key to the management of an acute esophageal varix hemorrhage is achievement of early hemostasis and prevention of rebleeding. The primary duty of Emergency Room staff is to resuscitate and stabilize patients who present with upper G.I. bleeds. Endoscopic examination is used to locate bleeding points and concurrent sclerotherapy is instituted when varices or other bleeding sites are visualized. Sclerotherapy is usually effective in controlling the initial bleed and reduces the risk of early rebleeding. Pharmacotherapy is sometimes used to control the bleed until endoscopy can be instituted. Balloon tamponade is most useful in providing temporary control of large bleeds until another strategy such as the transjugular intrahepatic portosystemic shunt (TIPS) procedure can be implemented. Procedures such as TIPS and combination therapies consisting of sclerotherapy with variceal ligation appear to be the management regimes of the future and are expected to reduce successfully the high mortality rates associated with variceal hemorrhage.

Introduction

Bleeding from esophageal varices is the most dramatic complication of portal hypertension. In North America, the most common underlying cause of portal hypertension is cirrhosis due to alcoholism. Approximately 30-35% of patients with cirrhosis will experience a variceal hemorrhage[1]. Increased portal pressure is the chief causal factor in the pathogenesis of esophageal varices and is dependent on portal blood flow and vascular resistance to flow. Thus, therapy of bleeding varices is geared towards reducing both flow and resistance as well as towards strengthening the variceal walls. The portal vein and its collaterals are shown in Figures 1 and 2.

WENDY KATES

These varices develop when portal pressure increases above 12 mmHg with 90% of bleeding points occurring within 2-3 cm of the junction[2]. Many portosystemic collaterals dilate in response to an elevated portal pressure but the ones situated at the gastro-esophageal junction are most

likely to bleed[1]. In this area, the veins have the highest wall tension, being superficial, large, and thin-walled[1]. The normal anatomy of the venous supply and submucous venous plexus of the gastro-esophageal junction is illustrated in Figures 1 and 3.

Patients with bleeding varices are generally poor surgical candidates during the acute episode because many are alcoholics with pre-existing complications, such as encephalopathy, ascites, malnutrition, renal failure, and coagulopathy[3]. A surgical procedure would further compromise liver function and so this emergency situation is best managed by non-surgical methods.

Most patients with varix hemorrhages present with hematemesis, melena, and signs of cirrhosis[1]. Due to the vast amount of bleeding during the acute episode, these patients are at risk of aspiration pneumonia, liver hypoxia, and encephalopathy[3]. Immediate management involves appropriate fluid resuscitation and the administration of blood and coagulation factors as necessary[1]. Gastric lavage is instituted to clear blood clots from the stomach and to facilitate endoscopy once the patient is stabilized[1]. Diagnosis is best made by flexible endoscopy; however, the source of an upper G.I. bleed is occasionally difficult to detect even with this procedure due to situations such as:

i) hypovolemia causing variceal collapse

ii) presence of blood which obscures vision

iii) bleeding from additional sites, which occurs in 50% of patients with varices[5].

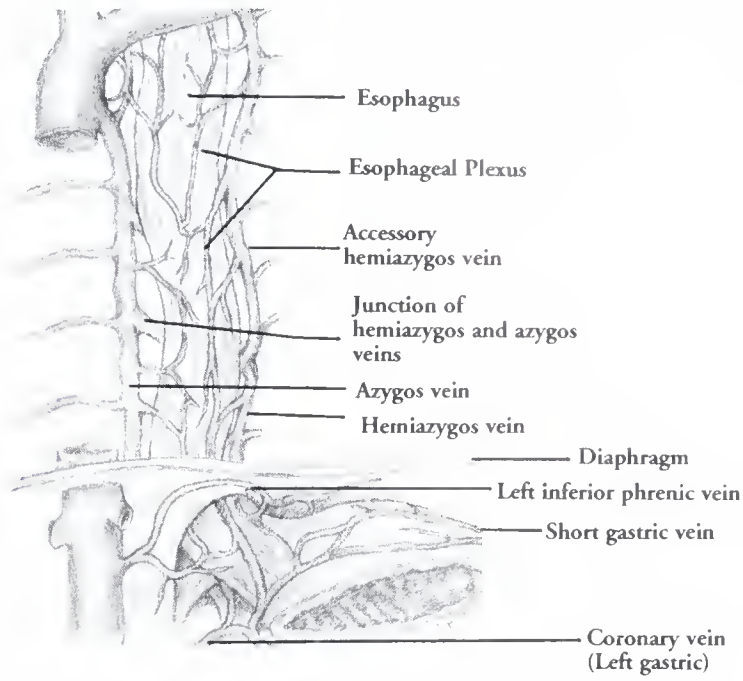

Figure 1: Venous supply of the esophagus (adapted from Netter[4]).

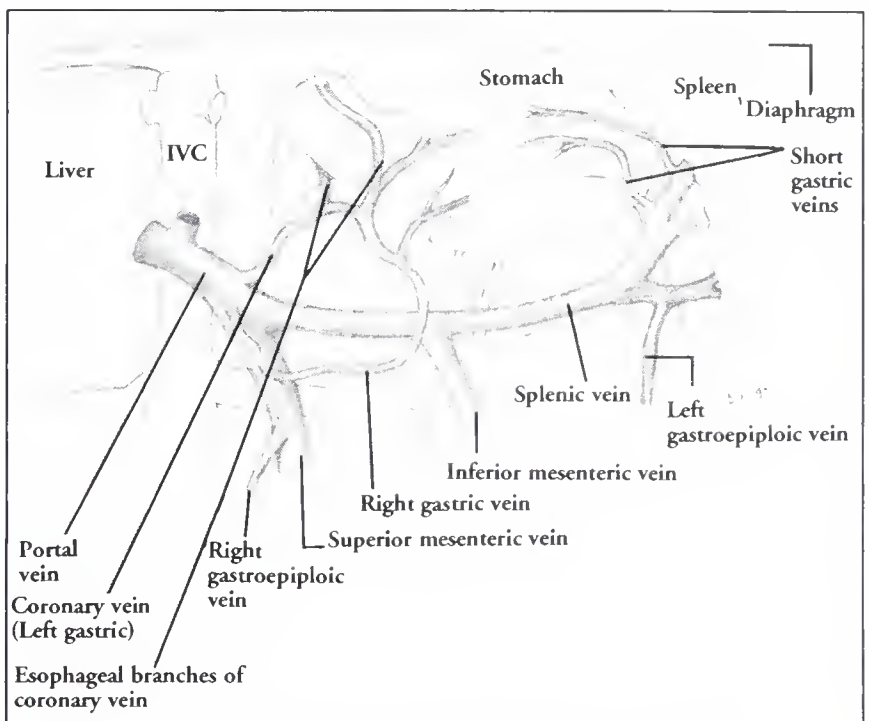

Figure 2: Normal portal venous system (adapted from Netter[4]).

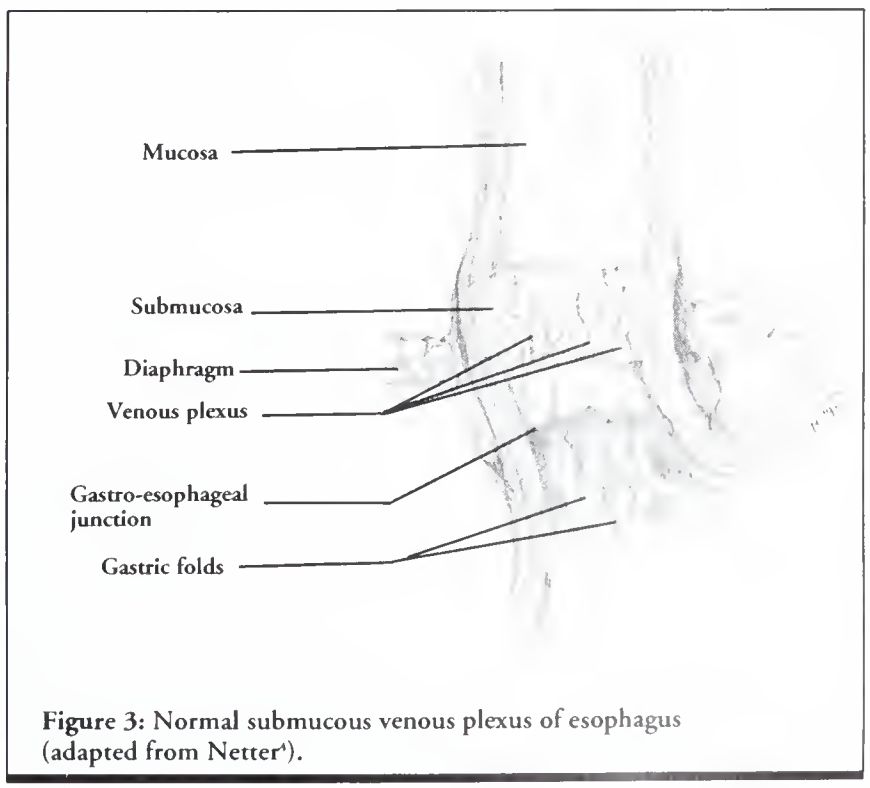

Figure 3: Normal submucous venous plexus of esophagus (adapted from Netter[4]).

The endoscope is used to examine the entire esophagus, stomach, and duodenum and diagnosis of bleeding varices is established if one or more of the following is seen:

i) adherent clots (rare)

ii) actively bleeding varix[3].

When active bleeding is not present, as is the case in more than 70% of patients, signs that correlate with recent hemorrhage or a risk of bleeding are then sought[3]. These signs include a red or bluish discolouration of the varix, "cherry-red spots", and red wale markings (exposed intima)[1].

A mortality rate of 20-50% is associated with the first bleed from varices and thus aggressive, prompt management is essential[2]. Management should also be aimed at preventing early rebleeding (hours to days) since 50% of patients rebleed within the first few days of admission[2]. Patients rebleed early because it takes weeks for the varices to thrombose after the initial bleed has stopped. Patients with severe liver disease classified as Child's class C (i.e. poor nutritional status, high serum bilirubin levels, low albumin levels, resistant ascites, and advanced neurological disorders) do worse than those with A or B disease regardless of any acute interventions[1]. The non-surgical approach to the management of acute esophageal varix hemorrhage can be divided into pharmacologic and non-pharmacologic therapies.

Pharmacotherapy

Theoretically, pharmacotherapy is the ideal form of therapy since it can be administered immediately without the need

of specialized equipment. The goal of pharmacotherapy is to reduce and then maintain portal pressure at less than 12 mmHg, thus promoting hemostasis[1]. This can be achieved by decreasing the resistance to flow within the liver and the portosystemic collateral network and by decreasing portal venous flow. Vasoconstrictors of the splanchnic vasculature are used to achieve this decrease in portal flow[1]. Intravenous vasopressin has been used for the past forty years and was the first drug to reduce portal flow successfully[3]. The current recommended infusion rate is 0.1-1.0 U/min, with 0.4 U/min being optimal[3]. However, vasoconstriction is not limited to the splanchnic bed and patients on vasopressin experience generalized vasoconstriction. As a result, major side effects may include myocardial ischemia, limb ischemia, and bowel and skin necrosis[3]. Studies have reported the occurrence of these side effects in 18%-30% of patients treated with vasopressin only[3,6-8]. Controlled studies have shown that vasopressin is only marginally better in the control of bleeding when compared to placebo (59% vs. 45%, $p > 0.05$)[2,9-12].

Many centres do not use vasopressin alone, but combine it with a vasodilator such as nitroglycerin. Nitroglycerin reduces the systemic vasoconstrictive effect of vasopressin while maintaining reduced flow in the splanchnic circulation. As well, nitroglycerin may also decrease the flow resistance within the liver, thus further reducing portal pressure[1]. The route of administration of nitroglycerin can be sublingual, intravenous, or transdermal without compromising its effectiveness[2]. Combination therapy is preferred over vasopressin alone due to a significant reduction in side effects and an enhanced control of bleeding[3].

Terlipressin, a triglycyl-lysine synthetic analogue of vasopressin, is sometimes used instead of vasopressin. The combination of terlipressin and nitroglycerin is very effective in achieving short-term hemostasis with minimal side effects. One study showed that 78% of actively bleeding patients were successfully treated with terlipressin and nitroglycerin and this benefit was still present 12 hours after initiation of therapy[13].

Somatostatin is another drug that has had recent support from various studies which show that it is just as effective as vasopressin and nitroglycerin[2,11,14,15]. Somatostatin and octreotide (a long-acting synthetic analogue of somatostatin) are vasoconstrictors that have very few side effects, even after several days of administration[16]. This fact is important since the risk of a rebleed is the highest during the first few days following admission, and also because the side effects of vasopressin increase greatly after the first 24-48 hours of use. However, these drugs are significantly more expensive than the other drug therapies and the role of octreotide still requires further study[1].

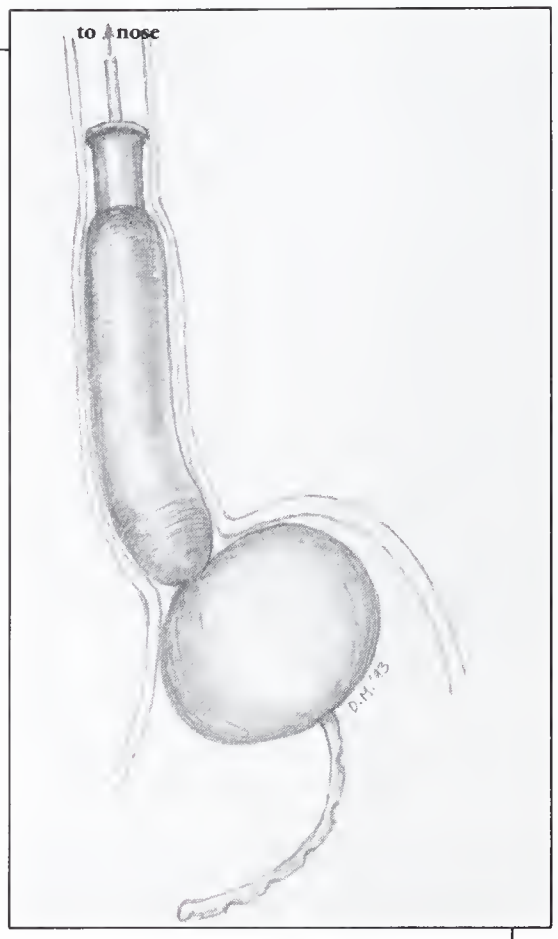

Figure 4: Proper position of tube during balloon tamponade[19].

Drugs that increase the lower esophageal sphincter (LES) pressure have also been investigated. A constriction of the LES may be able to reduce blood flow through the varices. These drugs include metoclopramide, domperidone, and pentagastrin. Studies to date have not been able to confirm any benefit offered by these medications[3,17,18].

Pharmacotherapy, in general, has had some success in arresting or reducing variceal hemorrhage; however, it has not been effective in massive bleeds or in the improvement of survival rates[3]. Its best role is probably a temporary one to give physicians extra time in order to institute other therapeutic modalities.

Non-Pharmacologic Therapy

Balloon Tamponade

Balloon tamponade has been used for the past forty years to control variceal bleeding[3]. This method involves the insertion of a tube into the stomach to allow close apposition of a balloon to the gastro-esophageal junction[19]. There are several different types of tube; the one with four lumens is most desirable since it reduces the risk of aspiration by allowing continuous suction from the esophagus[19]. Inflation of the balloon causes direct compression of the bleeding point or the veins feeding the bleeding point with subsequent hemostasis, as seen in Figure 4. Some studies have shown tamponade to control variceal bleeding in 80-90% of cases, accompanied by a 3% mortality rate that is directly attributable to the tube's placement within the esophagus (resulting in asphyxiation, esophageal perforation, or aspiration)[2,20]. However, this technique can eventually lead to mucosal damage (ischemia and ulceration) which may in itself predispose patients to a rebleed[3]. An application period of less than 12 hours should be adhered to[19].

Tamponade achieves only temporary hemostasis by direct compression and should be reserved for patients who are experiencing a massive hemorrhage, are being transferred to another centre, or are awaiting more definitive therapy[3]. In order to limit complications, only experienced personnel should insert such tubes. As well, since rebleeding rates are very high following deflation of the balloon, additional therapies such as sclerotherapy, surgery, or transjugular intrahepatic portosystemic shunts (TIPS) should be planned.

Endoscopic Sclerotherapy

Emergency injection sclerotherapy is the most widespread treatment used for an esophageal varix hemorrhage and can be administered during the initial diagnostic endoscopic evaluation[5]. Injections can be intravariceal or paravariceal or both, as shown in Figures 5a and 5b[21]. Commonly used sclerosants include 5% ethanolamine, 5% sodium morrhuate, and 1% polidocanol[3]. A well-trained endoscopist is needed to perform this procedure accurately and safely.

Hemostasis is achieved primarily by local edema due to the injection, causing compression of the bleeding vessels. Later, thrombosis of the varices and fibrosis of the vein walls further help to obliterate the vessels[1].

Injection sclerotherapy is the only therapy that has been shown conclusively to reduce the risk of early rebleeding[21]. However, rebleeding still occurs in 11-50% of patients after a single session[5]. This technique has also been shown to be similar to somatostatin in effectively controlling the primary bleed[5]. When compared to pharmacological management, sclerotherapy reduces the number of deaths by 25%[21]. There is a 1% risk of mortality associated directly with this procedure due to aspiration, septicemia, anaphylaxis, and esophageal perforation[1,5,21,22].

It is common practice to use alternative therapies after two sessions of sclerotherapy have failed to control bleeding. Pharmacotherapy is not indicated at this time and only such treatments as balloon tamponade, surgery, or TIPS should be considered[23]. Finally, sclerotherapy is a poor technique for the treatment of fundal varices[21]. These cases are more successfully managed with the use of tissue adhesives (e.g. n-butyl-2-cyanoacrylate) which harden upon contact with water and blood and are administered via the endoscope or with a TIPS procedure[21].

Endoscopic Ligation

Endoscopic ligation is a new technique that has its roots in the treatment of hemorrhoids. The procedure involves delivering an elastic "O"-ring around a portion of a varix by endoscopic means as shown in Figure 5c[21]. This technique does not carry the risk of complications caused by the injection of chemicals[3]. The banded varix sloughs off 3-7 days after treatment, leaving behind a shallow ulcer that re-epithelializes[21]. This ulcer does not increase the patient's risk of a rebleed[21]. Preliminary studies have suggested that endoscopic variceal ligation may be as effective as sclerotherapy with regard to survival rates and rebleeds, while being associated with minimal risks of non-bleeding complications[3,24-26]. Other recent studies have suggested that ligation together with low volume sclerotherapy may further increase survival[21,26,27].

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

The TIPS procedure reduces the resistance to flow in the portal system. As the name implies, it involves the formation of an intrahepatic shunt using a jugular vein as the initial access point. Using fluoroscopic means, a catheter is guided from a hepatic vein into a branch of the portal vein along an intrahepatic tract[28]. This tract is then dilated and a stent is introduced such that a portosystemic shunt is established. Preliminary results are promising with mortality rates of 0-14% over the first 30 days[28]. This therapy holds promise of becoming the treatment of choice for portal hypertension in the future[28]. However, much expertise is needed for its implementation and equipment costs are very high[3]. The TIPS insertion is sometimes combined with an embolization procedure which is used to induce thrombosis of a collateral vein such as the coronary vein[28].

Surgery

Emergency surgery does not generally have a role in the current acute treatment of an esophageal varix hemorrhage. It puts patients at a much greater risk of decompensation and may compromise future eligibility for liver transplantation[1].

There is a role for surgery when sclerotherapy fails or when there is thrombosis in the portal venous system[23]. However, surgical portosystemic shunts are likely to be replaced by the TIPS procedure because of mortality rates

Figure 5a: Paravariceal injection during endoscopic sclerotherapy[21].

Figure 5b: Intravariceal injection during endoscopic sclerotherapy[21].

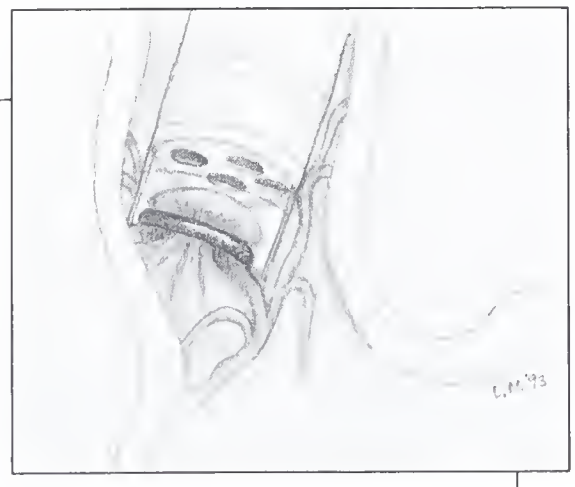

Figure 5c: Endoscopic ligation of an esophageal varix[21].

of 10-20% and a 25-50% incidence of encephalopathy associated with the former[23]. The Sugiura procedure (esophageal transection, extensive abdominothoracic devascularization, and splenectomy) has been shown in North American studies to carry mortality rates of 20%[23,29,30].

Liver transplantation as a long term management option is very promising with studies showing survival rates as high as 73% at 4 years[23,31] and 68% after 5 years[23,32] in patients with Child's class C cirrhosis. These figures are much better than those of portocaval shunts (31% at 5 years) or sclerotherapy (59% at 5 years)[23,31]. However, waiting lists are long and alcoholics must abstain from alcohol consumption for at least one year if they are to be considered as candidates for transplantation.

Prevention

Primary prophylaxis of bleeding esophageal varices is a major goal since high mortality rates still exist. In any one year, 12-22% of patients with cirrhosis and varices will experience their first bleed and, of these patients, 50% are likely to die[3].

Physicians must first be able to identify patients at risk of bleeding and then to administer prophylaxis that is economical and effective such that mortality is reduced. Endoscopy is the main tool for evaluating patients at risk. Pharmacotherapy with beta-blockers such as propranolol and nadolol has been shown to reduce the risk of a first bleed. Other drug therapies such as verapamil, gallopamil or isosorbide mononitrate in combination with propranolol have shown to decrease portal pressure but further studies remain to be done[23].

Prophylactic sclerotherapy has been shown by meta-analysis to reduce bleeding frequency significantly but studies have not shown a benefit for its use in primary prophylaxis[23]. This method may have a role in high risk patients who cannot tolerate propranolol therapy because of diabetes, asthma, or other potential adverse reactions[23].

If the liver disease is due to alcohol, then the best primary prophylactic therapy is abstinence. Liver cell size decreases, as does the size of the liver itself, once alcohol consumption is stopped. Furthermore, portal pressure may decrease and varices may disappear shortly after patients stop drinking.

Conclusion

As in all patients presenting with acute gastrointestinal hemorrhage, the initial management of patients presenting with an esophageal varix hemorrhage first involves resuscitation and stabilization with I.V. fluids. The subsequent detection of the bleeding site is accomplished by flexible upper G.I. endoscopy. Some centres treat the patient prior to endoscopy with pharmacotherapy such as vasopressin and nitroglycerin or somatostatin. Somatostatin can be continued several days after the bleed and, when used in conjunction with sclerotherapy, can prevent rebleeding. Massive hemorrhages are best controlled initially by balloon tamponade. This procedure is primarily used to allow physicians time for the institution of more definitive therapies and for pharmacotherapy or sclerotherapy failures.

Sclerotherapy remains the first-line treatment in most centres and can be administered during the initial diagnostic endoscopy. Sclerotherapy is the only treatment which has been shown to decrease early rebleeding rates. It is necessary for physicians to identify early sclerotherapy failures because the initiation of alternative methods can improve patient survival in this group.

Endoscopic ligation may soon overtake sclerotherapy as the treatment of choice because of fewer complications. Procedures such as TIPS and combination therapies such as sclerotherapy with ligation seem to be the management regimes of the future. Perhaps the best management in terms of economics and ease of administration is a preventative one such that portal hypertension and varices do not even appear. Unfortunately, abstinence from alcohol is difficult for many patients. For non-alcoholic chronic liver diseases, research is ongoing.

Acknowledgements

Figures shown are hand-drawn illustrations provided by the author (D.M.).

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Illustrations - Each figure should be designed to fit into an area of either one or two columns of text. Photographs and illustrations must be in black and white and of good quality. Colour will only be considered if the author or an outside sponsor is willing to pay the cost. The figures, including halftones and photographs, are to be numbered consecutively in Arabic numerals, and each one must be referred to in the text. Captions should be succinct but with sufficient detail.

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Review Process -For the editing process we require computer diskettes along with manuscripts. Please ensure that the name of the file and the program used to create the file are both indicated on the diskette. Accepted manuscripts will be edited to conform with UTMJ style and for correctness of grammar, syntax and punctuation. Adherence to gender neutral language is strongly encouraged. The first author will receive a copy of the edited manuscript or a galley proof prior to publication and is responsible for obtaining co-authors' approval of the changes. The printers will correct the proof **only for typographical errors** as indicated on the proof returned by the authors. Authors are asked to take the greatest care with the preparation of their papers. It will not be possible to make further alterations in the proof.

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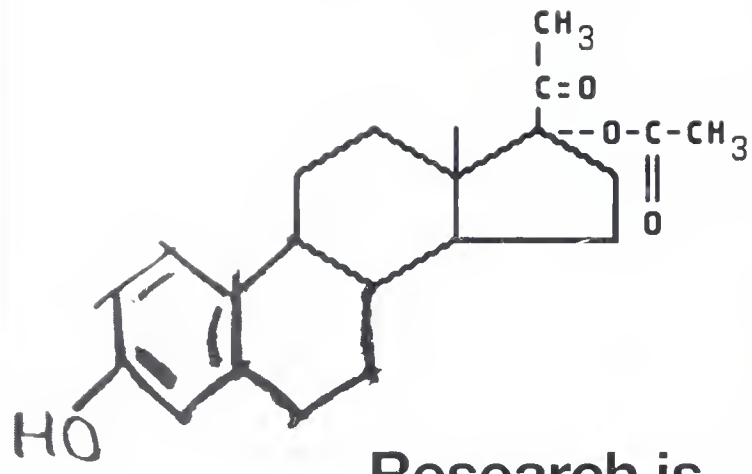

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Assessment and Management of Unresectable Pancreatic Cancer: A Review of the Current Literature

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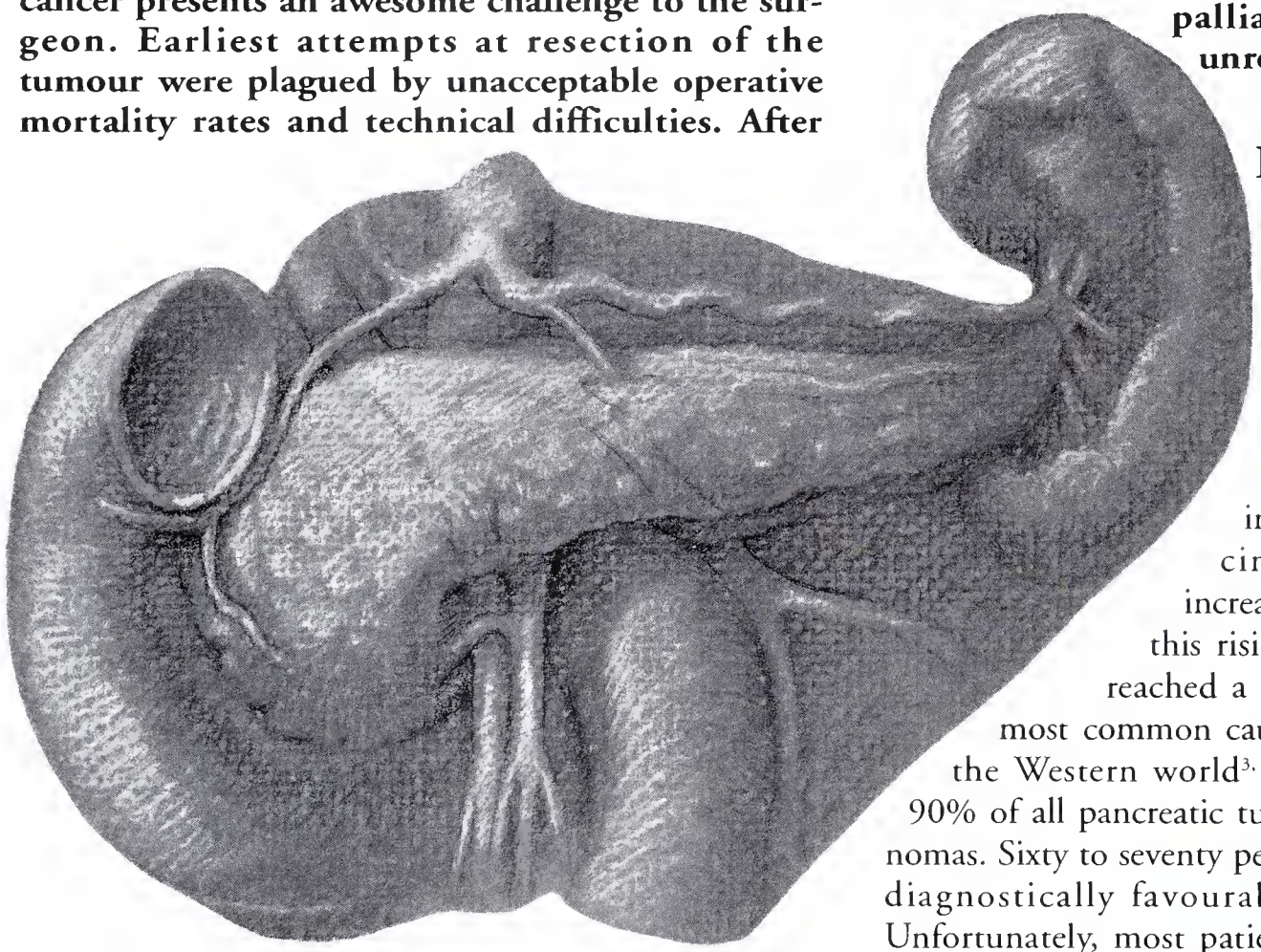
Abstract

Pancreatic cancer is a disease whose incidence has increased alarmingly over the past 40 years. In fact, it is now the fourth most common cause of cancer-related death in the Western world. Although surgery offers the only hope of cure in resectable disease, the procedure has not been without its problems. Due to its precarious location and invasive mode of spread, pancreatic cancer presents an awesome challenge to the surgeon. Earliest attempts at resection of the tumour were plagued by unacceptable operative mortality rates and technical difficulties. After almost a century of technical refinements, pancreaticoduodenectomy or "the Whipple procedure" has now met with limited success. Still, the unfortunate reality is that more than 80% of patients present with unresectable disease. As a result, the accurate preoperative assessment of resectability and the effective palliation of the patient with unresectable disease are two areas which have undergone intense research. This paper discusses the assessment of resectability with respect to recent advances in preoperative investigational modalities including: endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, computed tomography, magnetic resonance imaging, angiography, laparoscopy, peritoneal cytology, and endosonography. Finally, current approaches to the relief of pain and obstruction (bile duct and duodenal), as well as the role of adjuvant therapy are addressed in relation to the effective palliation of the patient with unresectable disease.



JUDY SHERWOOD

Introduction

Carcinoma of the pancreas is a worldwide problem. Its incidence over the past 40 years has doubled in Western Europe, tripled in the U.S.A., and quadrupled in Japan[1]. Until recently, the incidence in the U.S.A. of carcinoma of the pancreas had increased by 15% yearly[2]. Although this rising incidence appears to have reached a plateau, it is now the fourth most common cause of cancer-related death in the Western world[3, 4]. Histologically, more than 90% of all pancreatic tumours are ductal adenocarcinomas. Sixty to seventy percent of these originate in the diagnostically favourable head of the pancreas[5]. Unfortunately, most patients with adenocarcinoma of the head of the pancreas succumb to their to disease within a year of diagnosis[3]. In fact, fewer than 20% of patients with pancreatic cancer present with a potentially resectable tumour[1]. Overall, the 5 year survival is about 10%, although very few of these survivors are actually tumour free[2].

Resectability

In 1988, the American Committee for Staging of Cancer put forward a classification for cancer of the

pancreas (Table 1). Only T1 or T2 tumours are considered resectable. Tumours in the body or tail (which usually present late) and tumours greater than 4 cm (which are usually associated with local invasion) are seldom resectable. Forty-five percent of pancreatic cancers belong to stage II or III and cannot be removed despite the absence of distant metastases. Those with stage IV disease demonstrate metastases and are therefore poor candidates for resection.

The goal of the preoperative assessment in the patient with pancreatic cancer is to assess local invasion and distant spread. These two factors, in addition to an inability to withstand a major operation, are contraindications to resection. Until recently, it was believed that all patients older than 70 years were unable to withstand a pancreaticoduodenal resection. This bias has been challenged by recent reports of acceptable operative morbidity and mortality rates among selected patients over 70 years of age[7].

After a brief review of the progress that has been made in the surgical management of this disease, this paper will describe the various modalities used in the preoperative determination of resectability and will explore the issues in the management of those with unresectable disease.

Progress in Surgical Management

In 1935, Whipple and associates described a technique for the radical excision of tumours of the periampullary region including pancreatic cancer[6]. Unfortunately, initial attempts at resection in this region were plagued by discouraging operative mortality rates that were as high as 40%[7]. Over the years, the Whipple procedure has undergone numerous modifications and technical refinements in an attempt to improve postoperative survival. The original Whipple procedure bears little resemblance to what is now considered a pancreaticoduodenectomy[7]. Today, this procedure generally includes an en bloc removal of the gallbladder, common bile duct, duodenum, head of the pancreas over the portal vein and, generally, the antrum of the stomach, with or without an accompanying vagotomy. As recently as 1975, Shapiro questioned whether the then substantial operative mortality of 21% and dismal 5 year survival of 4% justified the use of pancreaticoduodenal resection for the management of pancreatic cancer[8]. Still, advocates insisted that resection afforded the only chance of cure. During the 1980s there was a dramatic decline in operative mortality with some centres reporting operative mortality rates less than 5% following pancreaticoduodenectomy. In addition, there was an apparent improvement in long-term survival. This led most surgeons to recommend pancreaticoduodenal resection for the management of patients with resectable pancreatic cancer[7]. In 1991, Cameron and associates[9] reported an encouraging actuarial 5 year survival rate of 21% in 81 patients with cancer of the head of the pancreas managed by pancreaticoduodenal resection. In fact, when the tumour had not involved lymph nodes (22 cases), the actuarial 5 year survival rate was an astonishing 57%.

Despite these promising reports with respect to improved post-operative survival rates, fewer than 20% of carcinomas of the head of the pancreas are resectable[1,10]. Carcinomas in the body and tail of the pancreas present even later and are thus rarely resectable at the time of detection. Pancreatic cancer spreads to regional lymph nodes, the liver, and the peritoneum, and locally invades vascular structures, the most important of which are the portal vein and its tributaries[11].

Assessment of Resectability

Surgical exploration with the hope of tumour resection was once the standard recommendation for most

Table 1

Staging of carcinoma of the pancreas (adapted from Warshaw et al. 1992)[17]

Stage	T	N	M	Description
I	1-2	0	0	no direct extension and no regional nodal involvement
II	3	0	0	direct extension into adjacent tissue but no lymph node involvement
III	1-3	1	0	regional lymph node involvement with or without direct tumour extension
IV	1-3	0-1	1	distant metastatic disease present

T1=no direct extension of the primary tumour beyond the pancreas.
T2=limited direct extension to duodenum, bile duct, or stomach.
T3=advanced direct extension, incompatible with surgical resection.

N0=regional lymph nodes not involved.
N1=regional lymph nodes involved.
M0=no distant metastases present.
M1=distant metastases present.

patients with pancreatic cancer[1,10]. The rationale behind this approach was that, in addition to providing an opportunity to make a tissue-based diagnosis and grossly assess resectability, palliation in the form of duodenal or biliary bypass could be offered in the event of intraoperatively discovered unresectable disease. With the advent of improved non-invasive preoperative staging techniques, this approach is no longer justified.

Table 2

Modalities used in the assessment of pancreatic cancer.

• Ultrasound (US)	• Angiography
• ERCP	• Laparoscopy
• CT	• Peritoneal Cytology
• MRI	• Endosonography (endoscopic US)

Recently, various investigational modalities including ultrasound, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), computed tomography (CT), magnetic resonance imaging (MRI), angiography, laparoscopy, peritoneal cytology, and endoscopic ultrasonography (endosonography) have been used to diagnose malignancy and determine resectability (Table 2). As each of these modalities continues to improve and as the newer technologies become more available, recommendations with regard to preoperative assessment will inevitably change.

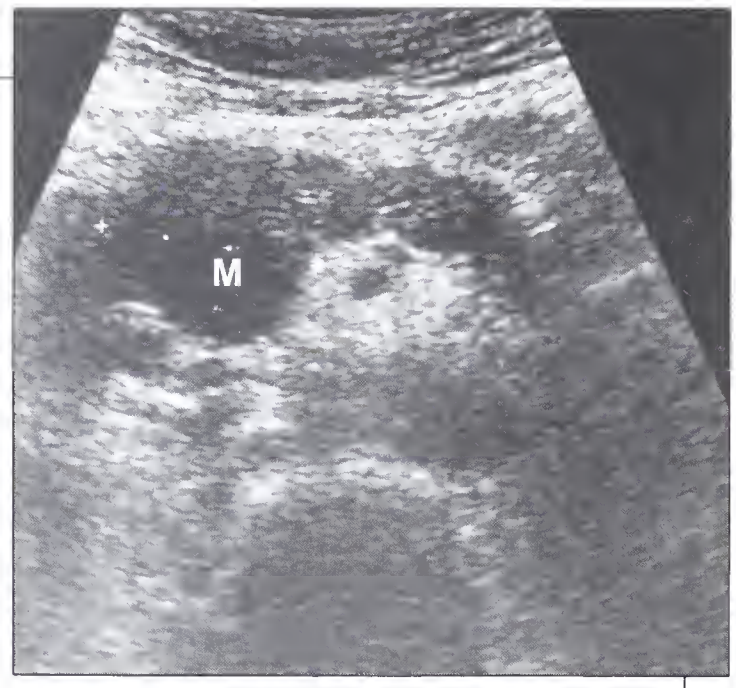


Figure 1: Transverse ultrasound scan of upper abdomen: Hypoechoic mass in the head of the pancreas **(M)**

1. Ultrasound

Currently, ultrasound remains the most readily available and least expensive of the imaging modalities (Figure 1). It is useful in both detection of pancreatic tumours and evaluation of extent of disease and bile duct dilatation. However, approximately 15%-20% of pancreatic ultrasound examinations are inadequate due to factors which prevent adequate resolution of the pancreas (e.g. bowel gas, obesity). Furthermore, the tail of the gland can only be delineated in 60%-70% of cases[5]. On the whole it is ineffective in determining nodal involvement or vessel encroachment. Therefore, ultrasound is not a dependable modality for determining unresectability unless the lesion is very large. Still, owing to a high tumour detection rate (accuracy and specificity as high as 80%-90%), ultrasound continues to be considered the best initial imaging method for screening of patients with clinical suspicion of pancreatic cancer[5].

2. Endoscopic Retrograde Cholangiopancreatography

ERCP has proven to be better than ultrasound and at least equal to if not better than computed tomography at diagnosing pancreatic cancer[12]. It is also useful, as is PTC, but with less morbidity, in determining the level of biliary obstruction which contributes to the determination of the surgical approach. Alone, however, it is not useful for staging as it is not helpful in determining metastases or nodal involvement[11].

3. Computed Tomography

This is an important tool in the staging of pancreatic cancer (Figure 2). Although many reports have been written about this modality in this context, the numerous studies often offer conflicting recommendations. Still, there is general agreement on the following issues:

1. CT is useful in determining unresectability due to hepatic or distant metastases, pre-pancreatic fascial extension, extension of tumour to contiguous structures, vascular encasement or invasion, local lymphadenopathy, and ascites[11].

2. CT predicts unresectability better than resectability. Warshaw[13] found CT to be 92% accurate in determining unresectability but only 45% accurate in determining resectability.

3. CT is not reliable for detecting liver metastases less than 2 cm in diameter. This is significant because one-third of patients with metastatic pancreatic cancer in the liver have deposits less than 2 cm in diameter[14,15].

4. CT is not reliable for detecting microscopic lymph node metastases. In fact, by the time lymph node involvement is seen on CT, there is often other evidence of unresectability.

5. CT does not detect small (1-2 mm) omental and peritoneal metastases which are found in 40% of patients without CT, MRI, or angiographic evidence of metastases[15,16].

4. Magnetic Resonance Imaging

So far, MRI has not proven to demonstrate any improvement over CT in assessment of resectability[11]. Considering its high cost, discomfort to the patient, and lack of availability, it is rarely used for this purpose.

Figure 2: Abdominal CT Scan - Transverse cuts

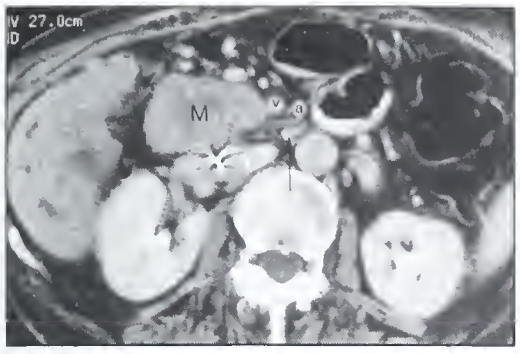


Figure 2a: Mass (M) in the head of the pancreas. Tumour extension (arrow) posterior to the superior mesenteric artery (a) and vein (v).

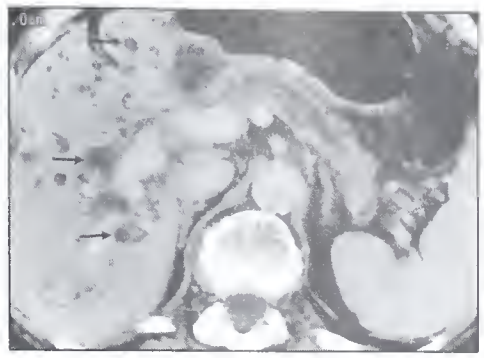


Figure 2b: Dilated pancreatic duct (PD) and dilated intrahepatic bile ducts (arrows) secondary to mass in the pancreatic head. Note: Figures 2a and 2b are of the same patient.

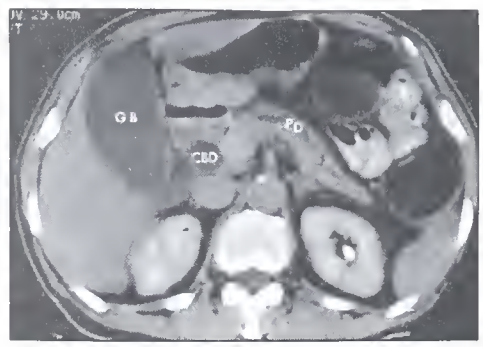


Figure 2c: Dilated pancreatic duct (PD), common bile duct (CBD) and gall bladder (GB) secondary to mass at the head of the pancreas. Grossly dilated gall bladder would likely be palpable and therefore give a positive Courvoisier's sign. Note: Figures 1 and 2c are of the same patient.

5. Angiography

Angiography is used to examine the coeliac and superior mesenteric circulation. It is generally agreed that angiography is not useful in determining tumour size or location, nor is it often helpful in detecting hepatic, peritoneal, or omental metastases, unless they are large[17]. However, angiography is helpful in detecting major vessel involvement[18]. Previous studies have found that CT and angiography are equivalent in their ability to demonstrate vascular involvement in individual patients, but found angiography to be superior on a "vessel-by-vessel" comparison[19]. More recent literature has debated this issue but it can be said that both tests are complementary and that when either or both are positive for unresectability, accuracy is 80%[20].

Other less appreciated benefits of angiography include:

1. Delineation of vascular abnormalities important to the consideration of resection in 15% of patients[21].

2. Evaluation of atherosclerotic changes in the coeliac or superior mesenteric arteries. This is significant in that severe atherosclerosis could indicate an unusual dependence on collateral circulation by the stomach, liver, spleen, or small intestine which could be compromised by the ligation of the pancreaticoduodenal artery during surgery[21].

6. Laparoscopy

In 1988, it was reported that 40% of patients without indication of metastases on CT or angiography proved to have small (less than 2 cm) hepatic, omental and peritoneal tumour deposits[22]. Understandably, preoperative laparoscopy has received a lot of enthusiasm. Combining the results of CT, angiography, and laparoscopy, Warshaw et al. identified 89% of the surgically proven unresectable cases preoperatively[22].

7. Peritoneal Cytology

Recently, studies have tried to assess the usefulness of this modality in the staging of pancreatic cancer. In a study by Warshaw et al.[13], only 10% of patients with a positive cytology in the context of a malignant diagnosis had resectable tumours. In comparison, 52% of patients with negative cytology and carcinoma of the pancreas were resectable. Although this difference was statistically significant, peritoneal cytology did not correlate with metastases or vascular involvement. This study also demonstrated that a previous biopsy of the pancreatic tumour may lead to the shedding of cancer cells and so make this modality less reliable. The usefulness of this modality still needs to be assessed.

8. Endosonography

As alluded to above, ultrasound accuracy declines with the presence of bowel gas and obesity. Endoscopically administered ultrasound, however, has been developed to overcome these problems in resolution. In the literature, this technique is demonstrating usefulness in the evaluation of regional nodal metastases and major vessel involvement[5] but it is not useful in the detection of distant metastases. Problems have arisen distinguishing hypoechoic lymph nodes from metastases or inflammatory changes. The addition of a pulsed Doppler with endosonography promises to enhance the detection of major vessel encasement. At the moment this is not a routinely used modality and thus also needs further investigation[11].

Table 3

Management issues for patients with unresectable pancreatic tumours.

- Relief of bile duct obstruction
- Relief of duodenal obstruction
- Relief of pain
- Adjuvant therapy

Management Alternatives in Unresectable Disease

In the palliation of patients with unresectable pancreatic cancer, there are a number of issues that need to be considered (Table 3).

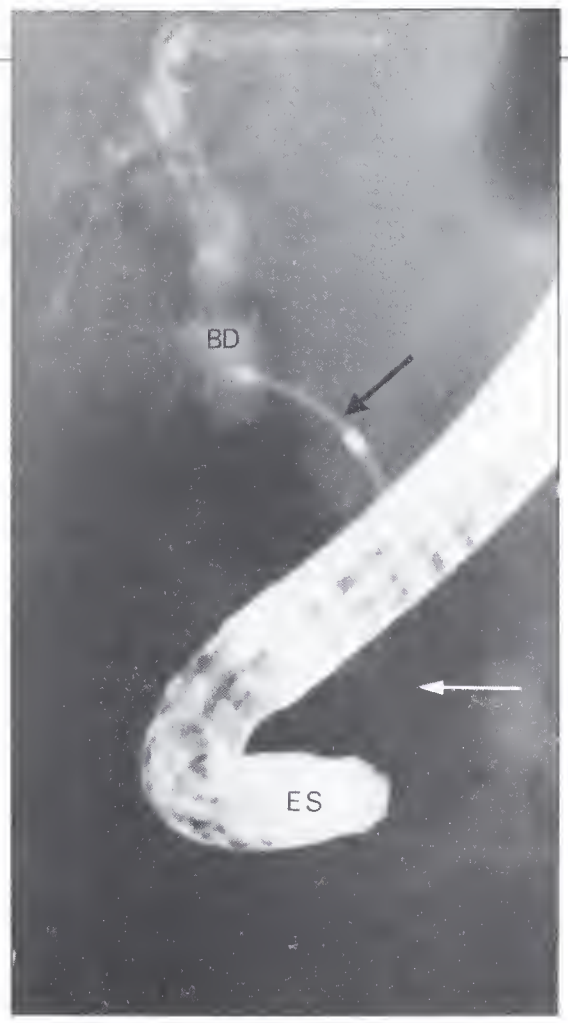


Figure 3a: Endoscope (ES) placed in duodenum. Guide wire (arrows) has been inserted into the common bile duct and contrast has been injected demonstrating bile duct dilation (BD) secondary to proximal obstruction in the pancreatic head.

Figure 3b: Stent (St) has now been placed in the common bile duct to relieve the obstruction at the head of the pancreas. Injected contrast outlines the dilated biliary tree (BT).

Figure 3: ERCP

1. Relief of bile duct obstruction

Jaundice is a sequela of bile duct obstruction. Bile duct obstruction can also lead to pruritus, malabsorption, ascending cholangitis, and liver and renal impairment. In order to relieve these serious causes of morbidity, various treatment modalities have been employed. Operative biliary bypass is an effective method of circumventing bile duct obstruction. However, the operative risk precludes this method in many patients. As an alternative, stents have been devised to be placed endoscopically in the common bile duct to preserve duct patency and bile flow (Figure 3). In comparison to endoscopically or percutaneously placed common bile duct stents, operative biliary bypass tends to have fewer late complications such as clogging but does demand a longer initial hospitalization. Surgical biliary bypass may be warranted in the patient who can tolerate such an operation and who has an unusually longer survival prognosis. This advice may change, however, as the technology for stents is rapidly improving. Already the management of choice in the inoperable patient, stenting provides effective relief of obstruction. Endoscopically placed stents appear to be more successful than percutaneously placed stents and also have lower rates of morbidity and mortality. The trouble with stents has been the risk of stent migration and clogging which necessitates restenting. Newer models are addressing this problem with apparent success[23]. Clinical trials comparing plastic and expandable metal stents are also currently underway. Expandable metal stents promise easier placement, decreased rates of stent occlusion, less migration, and less need for restenting. Earlier studies failed to show the advantage of expandable metal stents[24-26] but at least one prospective randomized controlled trial has shown expandable metal stents to be more cost effective when compared to their plastic counterparts[23].

2. Relief of duodenal obstruction

Duodenal obstruction is a common late complication of cancer in the head of the pancreas. For this reason, gastrojejunostomy used to be performed prophylactically if during investigational laparotomy an unresectable tumour was found. In patients with unresectable lesions who were diagnosed non-operatively, surgical bypass may still be warranted if tolerable. Obviously, relief of duodenal obstruction may never be necessary and therefore the prophylactic approach is no longer warranted in those who were non-invasively diagnosed as unresectable. Recently, endoscopic duodenal stenting has become available. An encouraging report supports the use of expandable metal stents in the relief of duodenal obstruction as safe and effective. In fact, patients in this study were all eating just 3-4 days after the procedure. At the present time, this modality is being investigated and needs to undergo more prospective randomized trials comparing it to surgical bypass[27].

3. Relief of pain

Pain is a presenting symptom in 70% - 90% of patients with pancreatic cancer[2]. Although it may settle after appropriate bypass or stenting, deep-seated back pain is present in 80-85% of patients with advanced stages of the disease[1, 28]. When exploratory laparotomy was more popular, ductal decompression was often performed at that time. Now that non-invasive diagnosis and assessment are possible, non-invasive relief of this pain has been sought. In recent years, opioid analgesics and percutaneous coeliac plexus blocks have been compared in the literature. Mercandante et al.[28] demonstrated that coeliac plexus block reduces opioid consumption in the control of pancreatic cancer pain in patients surviving

on average 51 days. Although traditional analgesic treatment was also shown to be effective, the decreased amounts needed after coeliac plexus block avoided the undesirable side effects inherent in the old regime of only opioids.

4. Adjuvant therapy

Although this is still a discouraging endeavour in oncology, there do appear to be two methods which provide statistically significant life extension, namely 5-FU and radiotherapy. However, one must weigh the morbidity (increased hospital visits, therapy side effects, and anxiety) inherent in these procedures with the only modest extensions in survival. Of particular promise is the use of endoscopically administered radiotherapy in conjunction with stenting. Techniques are now available to deliver radiation endoscopically through nasobiliary catheters prior to stent placement and external beam radiation; this appears to result in a longer survival than stenting alone[25,29].

Conclusion

An approach to the patient with suspected pancreatic cancer is outlined in Figure 4.

1. Assessment of resectability in the patient with cancer of the pancreas

Once diagnosis of cancer of the pancreas has been established, one must assess the extent of disease. Presence of metastases, vessel encroachment or invasion by tumour, or inoperability all preclude the use of a pancraticoduodenal resection. Metastases are best visualized with CT. If CT is inconclusive for vessel invasion in the absence of metastases, angiography may be warranted. If all of these measures are inconclusive, laparoscopy may be performed (if tolerable) to search for metastases. Finally, if laparoscopy is also equivocal, surgical exploration may be performed in the hopes of finding a resectable tumour. If the tumour is now deemed unresectable, palliative biliary and gastric bypass should be considered.

2. Management of the patient with unresectable cancer of the pancreas

Management of the patient once unresectability of the mass has been established should focus on pain management, relief of bile duct obstruction (endoscopically), and relief of gastric outlet and duodenal obstruction (surgical or endoscopic stenting). Other complications that one must be aware of are biliary stent migration or clogging, ascending cholangitis, abscess, and fistula.

Although resectability rates have improved over the years, pancreatic cancer is still rarely curable. Hopefully, continued progress in the areas of pre-operative diagnosis and assessment of the disease will lead to higher rates of resectability and cure. For now, a balanced and compassionate palliative management is all we can offer those with the all-too-common unresectable tumours.

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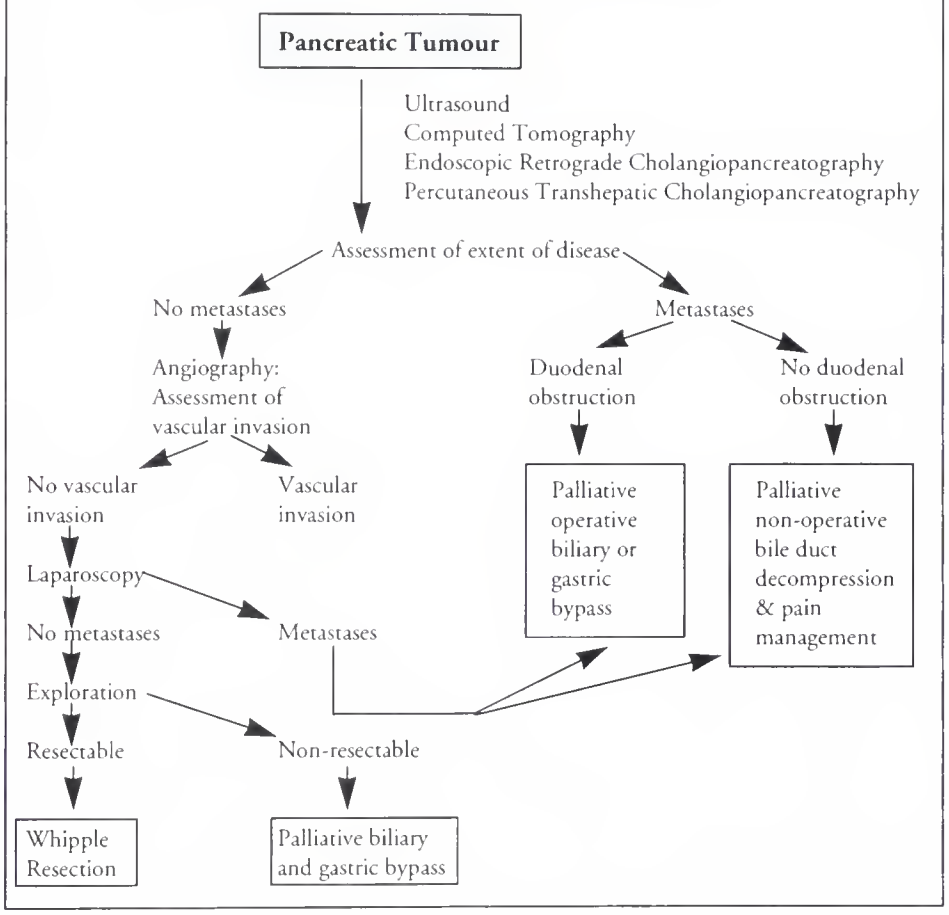
Figure 4
Algorithmic outline of an approach to the patient with pancreatic cancer. (From Karl RC et al, 1993[11].)



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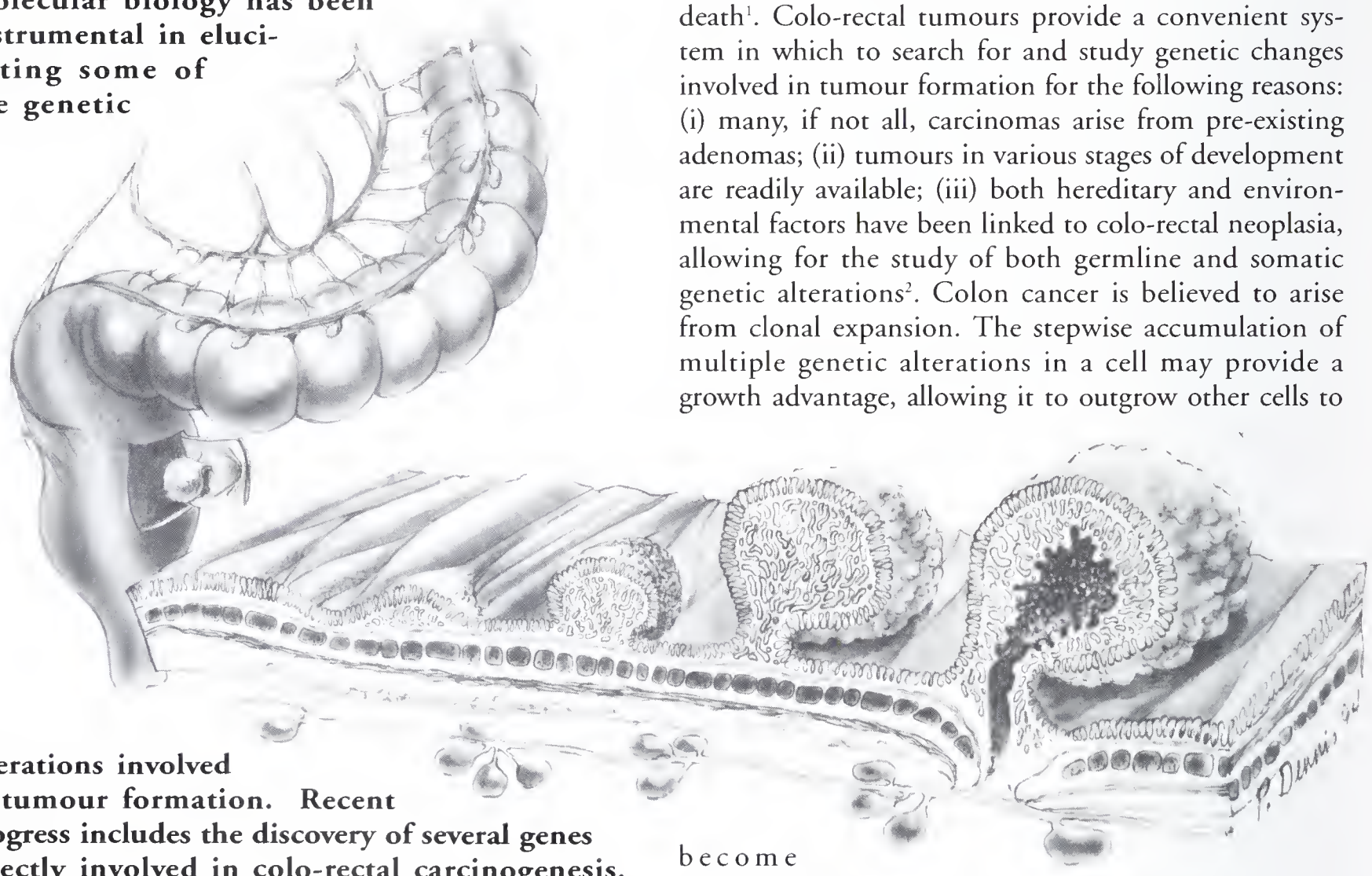
The Molecular Genetics of Colo-Rectal Neoplasia

Elizabeth Grigoriadis, B.Sc. (9T5)

Abstract

Molecular biology has been instrumental in elucidating some of the genetic alterations involved in tumour formation. Recent progress includes the discovery of several genes directly involved in colo-rectal carcinogenesis. Development of colon cancer is believed to take place by progression of normal epithelium to adenoma and carcinoma via a series of genetic alterations involving oncogenes such as *ras* and tumour suppressor genes, particularly those located on chromosomes 5q, 17p, and 18q. In addition, the newly discovered hMSH2 gene may contribute to tumour progression by rendering a subset of tumour cells hypermutable. In this paper, the genes involved in colo-rectal tumourigenesis are reviewed, some aspects of their prognostic significance are considered and a current model of colonic tumourigenesis is presented.



PAULETTE DENNIS

Introduction

Colo-rectal cancer is a major cause of morbidity and mortality in the western world. In Canada, about 3000 men and 2700 women died of the disease in 1991, making it the third most common cause of cancer death[1]. Colo-rectal tumours provide a convenient system in which to search for and study genetic changes involved in tumour formation for the following reasons: (i) many, if not all, carcinomas arise from pre-existing adenomas; (ii) tumours in various stages of development are readily available; (iii) both hereditary and environmental factors have been linked to colo-rectal neoplasia, allowing for the study of both germline and somatic genetic alterations[2]. Colon cancer is believed to arise from clonal expansion. The stepwise accumulation of multiple genetic alterations in a cell may provide a growth advantage, allowing it to outgrow other cells to become the predominant cell type constituting the neoplasm[2]. The intent of this paper is to review the current understanding of molecular genetics as it pertains to colo-rectal neoplasia. More specifically, the genes known to be involved are discussed, some aspects of their prognostic significance are considered, and a current model of colonic tumourigenesis is presented.

Cancer Genetics: Oncogenes and Tumour Suppressor Genes

The genetic alterations responsible for the transition to neoplasia may occur in two distinct types of genes: cellular oncogenes and tumour suppressor genes. Cellular oncogenes in their normal form are termed proto-oncogenes and they are believed to play an important role in cell growth and regulation. Oncogenes contribute to

malignant transformation when they become activated by point mutation, translocation, amplification, or loss of regulator sequences; hence they are dominantly acting[3]. The result of an activating mutation is to produce a constitutively active protein[4]. Oncogene activation, however, is not sufficient for the development of full malignancy. Genetic alterations also include the loss or inactivation of two or more tumour suppressor genes, which normally work to inhibit cell growth. Consequently, several mutations are necessary for cancer development and this is consistent with the epidemiology of colon cancer which indicates an age of onset in middle age or later to be most common[5].

The normal function of tumour suppressor genes is to suppress or control cellular growth. They differ from oncogenes in that inactivation via mutation or gene deletion is required for cancerous transformation to occur. Wild type alleles of such genes thus function to prevent or suppress tumourigenesis. Therefore, two separate mutational events are required to inactivate the gene. This is consistent with Knudson's "two hit" hypothesis[6] which has been used to explain the increased incidence of cancer in hereditary cancer syndromes. In such syndromes, Knudson postulated the first hit to be a defective gene inherited from a parent or a gene mutated in germ cell production. Such a gene would be present in all cells of the recipient. A second hit would therefore produce total inactivation of the gene. Cancer would occur at an increased frequency in this population because only one rather than two mutational events are needed to release the gene from its tumour suppressing effect. In the case of sporadic cancers, the tissue must suffer two hits, thereby explaining the lower rate of sporadic cancers versus that seen in hereditary syndromes. Some of the hereditary forms of cancer that helped to identify such tumour suppressor genes include Wilms' tumour, neurofibromatosis, retinoblastoma and familial adenomatous polyposis[4].

Genes Involved in Colo-Rectal Cancer

Neoplastic transformation of colonic mucosa is thought to occur as a result of a series of genetic alterations leading to the progressive disordering of the normal mechanisms controlling growth. Currently, genes identified as participating in colo-rectal carcinogenesis include the *ras* oncogene, which is a dominant type of oncogene, and the APC, p53, and DCC genes, which are tumour suppressor genes. These tumour suppressor genes were first implicated by karyotypic analysis which demonstrated non-random and consistent deletion of specific regions on chromosomes 5, 17 and 18 in cells derived from colo-rectal adenomas and carcinomas[7]. The possibility of involvement by additional, as yet unidentified, tumour suppressor genes is currently being investigated[8].

Recently, it has been postulated that a mutator phenotype resulting from a genetic alteration early on in carcinogenesis may lead to genetic instability[9]. Interestingly, Parsons et al.[9] found cells manifesting replication errors (RER+) in microsatellite sequences to be hypermutable. The increased mutability in these cells was associated with a profound defect in strand-specific mismatch repair. Tumours from patients with hereditary nonpolyposis colo-rectal cancer (HNPCC) have been shown to be RER+, suggesting that the gene responsible for HNPCC, probably the newly-discovered hMSH2[10,11], encodes a protein involved in mismatch repair[10,11]. However, further studies are still required to confirm this association.

The *Ras* Oncogenes

The *ras* oncogenes are a family comprised of three cellular genes, H-*ras*, K-*ras* and N-*ras*, and they are known to be mutated in a variety of human and animal tumours. Mutations are dominant and are known to occur in about 47% of colo-rectal carcinomas[12]. These involve highly conserved regions of the protein, preferentially those represented by codons 12, 13, 59, and 61 of the K-*ras* allele[13]. Such mutations are present in an equal percentage of villous adenomas and carcinomas (45% to 47%) but in only 4% of smaller tubular adenomas[12]. About 50% of colo-rectal carcinomas lack mutations in *ras* indicating that the adenoma-carcinoma progression is accomplished through another mechanism.

A normal *ras* gene encodes a membrane-associated guanine nucleotide-binding protein of 21 kD, termed p21. The protein product is thought to be involved in signal transduction in cellular proliferation and differentiation pathways[14]. Mutant *ras* genes result in a protein that is constitutively active; in other words, it maintains the activity of signal pathways at a constant level independent of actual external signals. The end result is a growth advantage that contributes to the development of a neoplasm[4].

Benhattar et al.[13] suggest K-*ras* mutations have prognostic significance in colo-rectal carcinoma. Their study revealed that 25% of patients with non-recurring carcinoma had mutations occurring within codons 12 and 13 of the K-*ras* gene compared to 71% in patients with recurrent colo-rectal neoplasia. Second, mutations other than GGT to GAT occurred almost exclusively in recurring tumours. Therefore, the authors concluded that in Dukes' B and C primary tumours, mutations other than GGT to GAT identify patients at very high risk for recurrence. The predictive value was not as strong in the Dukes' C group, however, possibly because in more advanced cancers, other prognostic parameters mask the predictive power of the *ras* mutation[13]. In contrast, Bell et al.[15] did not find mutations in K-*ras* codon 12 to

be of prognostic significance with respect to survival. However, when results were analyzed together with p53 over-expression (which was also not a prognostic indicator alone), median survival of patients was found to be less than half that of patients with either alteration alone or with no mutations. Hence screening for multiple genetic abnormalities in colo-rectal cancers excised at surgery may prove to be a useful tool in determining prognosis.

Other Oncogenes

Amplification of the c-*myc*, c-*myb* and c-*src* proto-oncogenes has also been implicated in some colo-rectal tumours[16-18]. These findings, however, are not consistent among all studies[19] and can occur in the absence of gross genetic change[20] and hence will not be further discussed here.

Chromosome 5 Deletion: The APC Gene

The 5q21 region, now known to contain the adenomatous polyposis coli (APC) gene, was found to be mutated or missing in individuals with familial adenomatous polyposis syndrome (FAP)[21]. FAP is inherited in an autosomal dominant fashion and afflicted individuals have hundreds of adenomatous colo-rectal polyps, with inevitable development of colo-rectal carcinoma unless the colon and rectum are removed. Gardner's syndrome (GS) is believed to be a variant of FAP in which additional abnormalities are found, including osteomas, desmoid tumours, and peri-ampullary carcinomas[4]. Early evidence linking GS to chromosome 5 came from cytogenetic studies of the peripheral blood of a patient with multiple abnormalities including colo-rectal polyps, colo-rectal carcinomas, and a large abdominal desmoid tumour. These studies revealed a deletion of part of the long arm of chromosome 5, at 5q13-22[22]. Subsequently, genetic linkage and restriction fragment length polymorphism (RFLP) analysis by various groups identified several chromosome 5q21 markers, tightly linked to disease in FAP and GS kindreds[23]. Further studies revealed that allelic losses from the same region were present in 30-40% of sporadic colo-rectal cancers[24] and in about 30% of sporadic colo-rectal adenomatous polyps[12].

Recently, a group in Utah[25] and one at Johns Hopkins[21,26] reported localizing the FAP gene at 5q21. The APC gene was shown to harbour germline mutations in patients with FAP and GS and was also shown to be mutated or deleted in sporadic colo-rectal carcinomas. A second gene named MCC (for "mutated in colo-rectal cancer"), was also found in the same general area as APC, however germline mutations in MCC were not found in FAP and GS patients. MCC mutations were only identified in sporadic colo-rectal carcinomas[27]. The significance of the MCC gene mutations in colo-rectal cancers is not yet known[4]. A more recent study of 41 colo-rectal lesions by Powell et al.[28] showed that 60% of colo-rectal cancers and 63% of adenomatous polyps had at least one somatic mutation of the APC gene. They found the overall pattern of mutations in sporadic colo-rectal polyps, cancers, and germline mutations in patients with FAP and GS to be the same. Given that APC mutations were noted in diminutive and large polyps as well as in cancers and that they were found to occur before *ras* mutations, the authors suggested that this genetic alteration is a rather early event in colonic carcinogenesis. It was suggested that mutation at one APC allele leads to epithelial hyperplasia and that mutations at other loci are required for neoplastic progression[2]. However, the exact role of the APC gene in polyp formation is not yet known[4].

The majority (59%) of APC mutations, are deletions or insertions of a small number of base pairs in the open reading frame of the gene[29]. Such frameshift mutations result in novel stop codons downstream from the shift, giving rise to truncated protein products. Such loss of function mutations are consistent with the idea that APC is a tumour suppressor gene[29]. Interestingly, patients with identical mutations could have either the Gardner's syndrome or familial adenomatous polyposis phenotype, and thus additional genetic or environmental influences are believed to play a role in determining the phenotype.

Improved markers for linkage analysis were developed as a result of the above work. Testing of these markers in the same families examined with older markers showed that a genetic diagnosis can be made in 95% of individuals, with a predicted accuracy greater than 98%[29]. In addition, it is now possible to detect mutant genes directly using various molecular techniques such as PCR[30]; however, this approach is currently limited by the great number of unique mutations occurring in various families[29].

Chromosome 17 Deletion: The p53 Gene

The p53 gene encodes a 53 kD nuclear phosphoprotein which is believed to control the activation of transcription by binding to DNA and allowing the cells to progress from G_0 / G_1 to S phase in the cell cycle[15]. The majority of p53 mutations produce an altered, non-functional protein lacking growth suppressor ability. Cells with a mutant p53 gene, therefore, have a growth advantage. The mutant gene has been found to be hyperstable with a prolonged half-life, rendering it capable of forming complexes with and inactivating the wild-type gene; hence mutant p53 can dominantly transform cells[31].

The p53 gene is the most commonly altered gene in human tumours and has been associated with a variety

of neoplasms including breast, lung and colo-rectal carcinomas[15,32]. It is the gene that underlies the cancer susceptibility in Li-Fraumeni syndrome[33]. Deletions from the short arm of chromosome 17 (17p) occur in 75% of colon cancers[34]. One of the most important features of this finding is that the deletions are significantly associated with invasive tumours rather than with adenomas or dysplastic but not frankly invasive lesions[12]. This pattern is in contrast to that observed in the *ras* oncogene and chromosome 5q and parallels that seen in chromosome 18 (see below). These findings suggest an association of 17p loss and invasive phenotype. In sporadic colon cancer, researchers have found that one copy of the p53 gene is often inactivated by point mutation whereas the other copy is frequently deleted[35]. Yin et al.[36] also found this mechanism to be operative in neoplasia associated with ulcerative colitis (UC) and Burmer et al.[37] suggest that in such tumours, alterations of the p53 gene may occur earlier than in sporadic colorectal carcinoma.

The p53 gene localizes to chromosome 17p and although it has been called a tumour suppressor gene, it does not behave like a typical tumour suppressor gene. Both alleles need not be inactivated before an effect on growth control is seen. A point mutation of one p53 allele can result in alterations in the control of growth through a dominant negative effect of the mutant allele on the remaining wild-type allele[38].

The sites of mutations in p53 are not random but cluster into particular areas or "hotspots" in highly conserved and probably vital regions of the protein[39]. It has also been shown that different p53 mutations produce proteins that have different properties with regard to their ability to change cell growth. This has led to speculation that different p53 mutant alleles may have different biological activities and, therefore, different prognostic implications in human tumours[4].

Chromosome 18 Deletions: The DCC Gene

Fearon et al.[40] cloned a gene located on the long arm of chromosome 18 and named it the DCC or "deleted in colo-rectal carcinoma" gene. Chromosome 18 gene deletions are seen in 73% of malignant tumours and 11% of nonmalignant adenomas[12]. Correspondingly, DCC gene expression has been found to be reduced or absent in colo-rectal carcinomas relative to expression in normal colonic mucosa[40]. The protein structure corresponding to the DCC gene sequence is very similar to that of neural crest adhesion molecules[2] a class of cell surface glycoproteins of the immunoglobulin superfamily[4]. These molecules are involved in cell-to-cell communication and the loss in communication that would result from DCC gene deletion may contribute to the abnormal behaviour of malignant cells.

Chromosome 2 Mutations: The hMSH2 Gene

HNPCC is a familial cancer predisposition syndrome accounting for 6% of the total colo-rectal cancer burden[41]. It is inherited in an autosomal dominant pattern. Affected individuals develop tumours of the colon, endometrium, ovary, and other organs, often before the age of fifty[41]. Recently, the gene believed responsible for HNPCC, called hMSH2, was identified on the short arm of chromosome 2 (2p)[10,11]. This gene is likely a homologue of the bacterial MutS gene whose protein product is responsible for mismatch recognition and initiation of methyl-directed mismatch repair[10,11]. Defects in this repair pathway are among the strongest mutator mutations identified in bacterial systems thus far[9]. Consequently, alterations of the hMSH2 gene are believed to result in defective mismatch repair, rendering affected cells hypermutable[10,11]. Interestingly, alterations in this gene cause replication errors in microsatellites of tumour cells only; normal cells in individuals with HNPCC are not affected[11]. In addition, although characteristic of HNPCC, the RER+ phenotype is also found in tumours from patients who are unlikely to have HNPCC on the basis of age and family history[42]. Hence it is likely that mutations in the hMSH2 gene cause a dominant mutator phenotype and are responsible for the rapid progression of some tumour subtypes.

Role of Gene Loss and Mutation in Colon Cancer Progression

Vogelstein et al.[12] studied the genetic alterations involved in colo-rectal tumour progression. They looked at four genetic alterations (*ras* gene mutations and allelic deletions of chromosomes 5, 17, and 18) in tumours representing various stages of neoplastic development. Their findings revealed that *ras* oncogene and chromosome 5 allele losses occur earlier in the adenoma - to - carcinoma sequence and chromosome 17 and 18 allele losses occur later, with 18q allelic deletions typically preceding 17p deletions. *Ras* oncogene and APC gene mutations are thus believed to be early events associated with the initiation of colo-rectal tumourigenesis, with APC gene alterations typically occurring before *ras* gene mutations[28], while p53 and DCC gene losses are believed to be late events implicated with tumour progression. Exceptions to this order clearly exist, however, and it has been emphasized that it is the accumulation and not the order of these changes that is important[2]. Furthermore, Fearon and Vogelstein[2] stated that alterations in the four genes were not sufficient for progression to malignancy; their analysis showed that at least one additional allelic deletion was required, with a median of four or five losses per tumour. Thus the number of genetic alterations sufficient for tumourigenesis is unknown and this number may vary depending on the population.

The loss of methyl groups in DNA has also been shown to occur early in colon cancer development[2]. Hypomethylation is known to cause consistent differentiation from hyperproliferative epithelium to adenomatous epithelium in patients with polyposis[43]. The cause of this loss is unknown but hypomethylation has been shown to inhibit chromosome condensation and this might lead to mitotic nondisjunction[44]. DNA hypomethylation may therefore also contribute to the chromosomal abnormalities of cancer cells (see Figure 1).

Some authors[10] suggest that the multiple independent mutations required for neoplastic transformation cited above are excessively high to be accounted for by the normal frequency of spontaneous mutations in cells. Mismatch repair defects resulting from hMSH2 gene inactivation may serve to accelerate tumour progression by allowing the cell to rapidly accumulate spontaneous mutations such as *ras,* p53, and DCC[11]. This increased mutation rate and associated genomic instability may underlie the development of HNPCC and RER+ sporadic tumours.

erably worse prognosis than did patients with fewer deletions. Hence, tumour allelotype may provide a molecular tool for improved estimation of prognosis in patients with colo-rectal carcinoma.

Conclusion

Molecular biology has helped scientists to understand better the genetic basis of carcinogenesis. The importance of the cumulative effects of mutations in the development and progression of colo-rectal malignancies has been supported by a number of studies. The identification of more common genetic alterations such as p53 mutation or screening for multiple genetic lesions would make genetic screening of stool samples or gene therapy a viable option. In addition, when the biochemical aberrations resulting from such genetic defects are known, knowledge-based chemotherapy, i.e. drugs which block the activity of mutated oncogenes or which mimic the effects of p53 activity, may prove

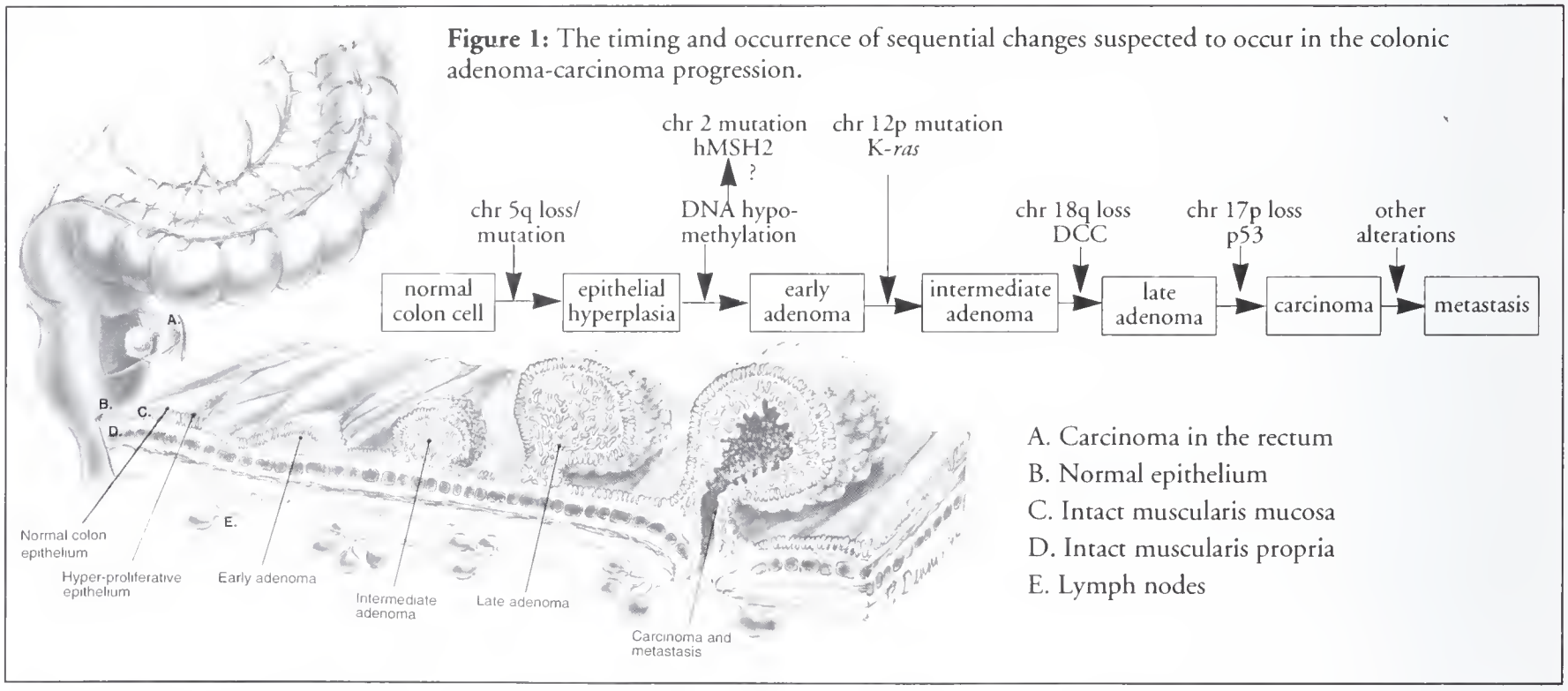


Figure 1: The timing and occurrence of sequential changes suspected to occur in the colonic adenoma-carcinoma progression.

A. Carcinoma in the rectum
B. Normal epithelium
C. Intact muscularis mucosa
D. Intact muscularis propria
E. Lymph nodes

Studies indicate that specific gene deletions and a high number of mutations per tumour are associated not only with a more malignant phenotype pathologically, but also with a worse clinical prognosis[4]. For example, Kern et al[45]. compared the clinical courses of patients with gene deletions in their tumours and found that patients with chromosome 17 or 18 gene deletion or a greater than average number of allele losses per tumour had a significantly increased risk of developing metastatic disease. Such gene deletions were found to be prognostic indicators of decreased survival in patients with Dukes' B and C carcinoma. Interestingly, the presence of chromosome 5 deletion and *ras* mutations did not have an effect on metastasis or survival. Similarly, Vogelstein et al.[24] found that patients with more than the median percentage of allelic deletions had a considhighly successful as therapy. It is also likely the future will reveal combinations of oncogenes and tumour suppressor genes that have a high invasive or metastatic potential. Early screening for these combinations via genetic probes would be of great prognostic value and would facilitate earlier and hence more effective intervention.

The pathogenesis of colo-rectal cancer is now better understood on a molecular level. Undoubtedly, mutations at other loci such as in hMSH2-dependent mismatch repair pathway genes will also be found to play a role in colo-rectal tumourigenesis. Eventually, the missing pieces of the tumour genetic jigsaw-puzzle will be found.

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The Role of Diet in Prostate Cancer

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Abstract

Prostate cancer constitutes a significant cause of mortality in North America and certain European countries. However, the disease frequency in East Asian populations, particularly Japan, is much lower, despite similar rates of "latent" histological lesions. These observations, along with results of migrant population studies, suggest that environmental influences, such as diet, may be important in the development of prostate cancer and perhaps in its progression to late stage disease. Interest has focussed on the possible roles of dietary fat and, more recently, biologically active food-derived compounds such as phyto-estrogens and mammalian lignans. Despite vigorous research, investigators have been unable to demonstrate a consistent association between fat intake and prostate cancer, and a causal relationship remains uncertain. Phyto-estrogens and mammalian lignans are either found in or derived from food products such as soymeal and certain grains, both of which comprise a significant proportion of the Japanese diet. Moreover, the serum and urine concentrations of phyto-estrogens and mammalian lignans are significantly higher in Japanese subjects than in people from Western nations. These data, as well as in vitro evidence of specific anti-tumor properties exerted by these compounds, support the hypothesis that certain dietary factors confer protection against prostate cancer, and thus are at least partially responsible for the wide geographic variation in the frequency of this disease.

Introduction

Next to lung cancer, carcinoma of the prostate is the leading cancer killer in North American males; it currently accounts for 21% of newly diagnosed cancers and 12% of deaths due to cancer in Canadian men[1]. In a worldwide comparison, these statistics place Canada among other high-risk nations of the western hemisphere, such as the United States and certain Scandinavian countries[2]. The incidence of prostate cancer has risen dramatically in these countries in recent years, probably due largely to the identification of histological neoplastic foci in tissue obtained during increasingly common transurethral prostatectomy procedures for benign prostatic hypertrophy. However, prostate cancer mortality rates have also increased significantly over the same time period[3], a trend which is more difficult to attribute to artifactual causes.

Other countries, specifically those along the Asian Pacific Rim, enjoy markedly lower rates of prostate cancer. For example, the incidence of prostate cancer in Japan is one tenth that of Canada's, and on a per capita basis, one fifth as many Japanese males die from the disease compared to their Canadian counterparts[2]. This wide geographical variation suggests that a deleterious environmental influence, particularly one inherent in a western lifestyle, may contribute to this disease process. This hypothesis is further supported by migrant population studies[4,5] in which subjects who have emigrated from an area of relatively low prostate cancer frequency to one of high frequency incur the substantially greater risk characteristic of the adopted country.

Diet is an environmental feature which varies significantly among different cultures, and therefore among different geographic regions. Based on epidemiologic data, a number of dietary factors have been implicated in either the development or prevention of prostate cancer. These substances include macronutrients such as fat and protein, vegetable components such as vitamin A and beta-carotene, and dietary minerals such as zinc and selenium[6]. In general, among the macronutrients, fat intake appears to be more strongly associated with prostate cancer and thus has received more attention. In contrast, data linking particular micronutrients to prostate cancer are inconsistent and relatively weak. Furthermore, there is no well-established animal model of prostate cancer through which the effects of dietary manipulation have been studied experimentally. For these reasons, very little is known about the effects of diet on the natural course of prostate cancer.

Because the pathogenesis of prostate cancer is believed to at least partially involve hormonal mechanisms, attention has turned toward dietary factors which may be capable of exploiting such pathways. This paper outlines the possible roles of two distinctly different dietary constituents currently receiving considerable attention in the relevant scientific literature, namely dietary fat and two classes of biologically active diphenols, the phytoestrogens and the mammalian lignans. As discussed in greater detail below, the latter two groups of compounds possess a wide array of properties, some of which may render them capable of influencing prostate cancer throughout the pathogenetic spectrum of initial malignant transformation to late-stage disease.

Natural History of Prostate Cancer

The cause of prostate cancer is unknown, but likely involves a combination of genetic, hormonal and environmental influences[2]. First- and second-degree relatives of men with prostate cancer are more likely to develop the disease than are age-matched controls (relative risk 2.0 and 1.7, respectively)[7], providing supportive evidence of a genetic influence. However, no specific genetic marker which consistently segregates with the disease has yet been identified.

Normal prostatic tissue is dependent on the trophic influence of male sex hormones (androgens) for growth and proliferation, and to some extent, neoplastic prostatic epithelial tissue retains this feature. This hormonal dependence underlies the rationale for therapies such as orchiectomy or hormonal anti-androgen treatment aimed at blocking the trophic androgenic stimulation which is believed to play a role in the transformation of normal prostate epithelium to malignant tissue. However, while these methods are generally effective in reducing the size of prostatic neoplasms, the majority of lesions not only recur within a mean time period of 15-18 months, but do so in a form which is resistant to similar hormonal manipulation[2]. Thus hormonal factors appear to be important in the initial malignant transformation of prostatic tissue, but the subsequent maintenance and growth of clinically invasive neoplastic foci appears in most cases to be independent of hormonal control.

This characteristic shift from androgen dependence to androgen independence represents a major barrier to successful treatment of prostate cancer, at least via methods which employ hormonal manipulation. The mechanisms responsible for this transformation have not been elucidated, but presumably involve modulation of the biochemical pathways responsible for maintaining hormonal control over prostatic epithelial cell function, ranging from abnormalities in cell surface androgen receptors to mutations in a putative nuclear oncogene, in a tumor suppressor gene, or in DNA which encodes cell surface androgen receptors[2].

The frequency of both clinically invasive prostate cancer as well as occult histological carcinoma increases steadily with age[3]. Interestingly, small foci of histological adenocarcinoma (i.e. "latent" cancer) are present in a substantial proportion of young asymptomatic men. Sakr et al.[8] examined the prostates of male trauma casualties at

autopsy and identified small foci of histological cancer in 27% and 34% of patients in their fourth and fifth decade of life, respectively. Such lesions are believed to represent an early stage in the progression toward clinically evident prostate cancer, and obviously may exist for several years, even decades, before undergoing a transformation (possibly influenced by environmental factors) into a more invasive neoplasm. In contrast to the frequency of the clinical, infiltrative type of prostate cancer, the frequency of latent, histological foci of cancer shows little variation among different geographic populations[9]. This phenomenon of similar frequency of latent, but not symptomatic, disease across diverse cultures suggests that endogenous influences (such as genetics) may play a greater role in the initiation of the neoplasm, whereas exogenous factors (such as diet) may be more important in the progression to invasive disease.

Dietary Fat Consumption and Prostate Cancer

Dietary fat consumption may influence the development of prostate cancer. A large number of case-control studies have examined the relationship between fat intake and the risk of developing prostate cancer. Some[10-12] have found evidence of a positive correlation, while others[13-15] have not. Many of these studies, however, were fraught with a traditional weakness inherent in a case-control design, namely the risk of recall bias when dietary data are collected after the diagnosis of cancer. Still, prospective cohort studies[16,17] which sought to overcome this limitation in study design have been unable to provide conclusive evidence of a link between total fat intake and prostate cancer; however, one such study[18] has shown a significant association between *animal* fat consumption and advanced prostate cancer.

Not surprisingly, the mechanisms through which fat ingestion may influence prostate cancer have not been clearly demonstrated. Possibilities range from the concomitant ingestion and subsequent effect of carcinogens formed during the cooking of red meat[19] to indirect mechanisms such as a fat-induced rise in serum androgen levels which could influence the growth and progression of androgen-dependent forms of neoplastic foci. However, the limited data available do not support a simple relationship between serum testosterone levels and clinically overt prostate cancer[20]. Alternatively (or additively), specific types of essential fatty acids could conceivably affect the response of prostatic tissue to testosterone or facilitate the formation of free radicals, highly reactive substances which can damage DNA and lead to malignancy[21].

Table 1

Mammalian lignan production from various foods (µg/100 g, wet weight)

FOOD GROUP	MEAN
Cereals	359
Triticale	924
Wheat	490
Purple Rice	420
Oats	340
Brown Rice	297
Sorghum	255
Corn	230
Rye	160
Barley	115
Cereal Brans	486
Oat Bran	651
Corn Bran	648
Wheat Bran	567
Barley Bran	383
Rice Bran	181
Defatted Flaxseed	67,541
Flaxseed	52,679
Other Oilseeds	638
Legumes	562
Vegetables	144
Fruits	84

Adapted from Thompson LU, et al.[26]

Phyto-Estrogens and Mammalian Lignans in Prostate Cancer

The lack of a strong etiologic association between dietary fat and prostate cancer suggests that other environmental factors may be more important in the pathogenesis of this disease. Recently, attention has focussed on the role of putative anti-carcinogenic substances in various foods, particularly those consumed in significant amounts by populations with a low incidence of prostate cancer. Two structurally similar classes of compounds, namely the phyto-estrogens and the mammalian lignans, are either contained in or metabolized from certain foods, and have been shown experimentally to exert a myriad of biological effects on cells. The diphenol structure of these substances renders them chemically analogous to synthetic estrogens, which have been used clinically to treat certain forms of cancer[22]. Like synthetic estrogens, mammalian lignans and phyto-estrogens have been shown to possess anti-estrogenic properties[23], which may have relevance in modulating both tumorigenesis as well as the susceptibility of prostate cancer to hormonal treatment. The recent demonstration[24] that one phyto-estrogen, genistein, inhibits the growth of neoplastic prostatic cells in vitro may be related to such hormonal properties, or may involve distinct anti-cancer mechanisms, as discussed in greater detail below.

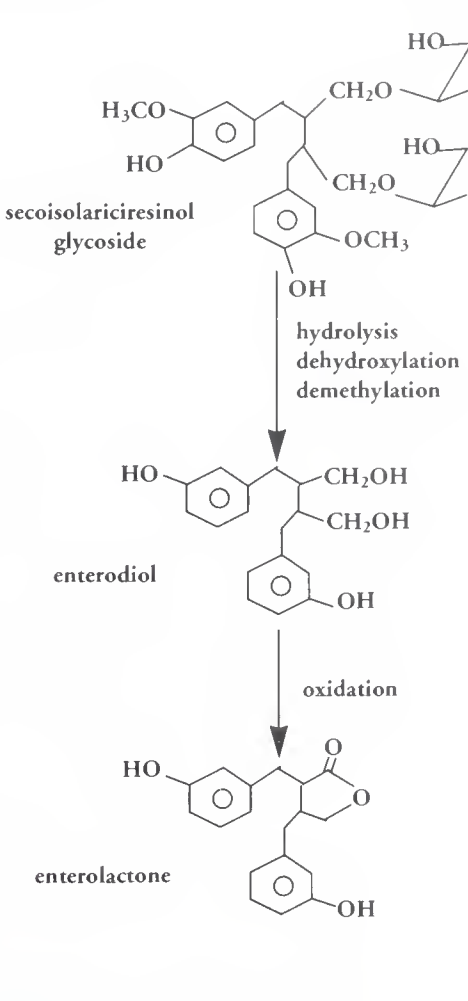
In contrast to Western dietary patterns, Japanese people consume large amounts of soy products such as tofu and soy beans which are abundant sources of phyto-estrogens. Adlercreutz et al. recently compared the plasma

levels of various phyto-estrogens in Japanese and Finnish men (n=14 from each country)[25] and found they were significantly (7 to 110 times) higher in the former group, providing further support for an inhibitory effect of these substances on prostate cancer.

Mammalian lignans are compounds derived from dietary glycoside precursors found in varying proportions in certain plant foods (Table 1), particularly grains and fibre-rich substances. Flaxseed, also known as linseed, is an especially rich source. The enzymatic activity of enteric microbial flora is required to convert the inactive dietary precursor, secoisolariciresinol glycoside, to biologically active mammalian lignans, such as enterodiol and enterolactone[27] (see Figure 1). These latter compounds are similar in structure to phyto-estrogens[28]. It thus seems plausible that mammalian lignans could play a role similar to that proposed for phyto-estrogens, namely protecting against or inhibiting the growth of prostatic cancer. Based on this hypothesis, Jenkins et al. are presently studying the effect of a diet high in flaxseed on the progression of established prostatic cancer. Preliminary results in a small number of patients suggest that flax consumption may be associated with a slowing in the growth of invasive disease, as reflected by a reduction in the rise of prostate specific antigen, a serum marker of tumor burden[29].

Figure 1

Proposed scheme for formation of the active mammalian lignans enterodiol and enterolactone from inactive plant glycoside. The stereochemical configuration of the parent sugar and the precise reaction mechanism have yet to be elucidated.



Adapted from Axelson M, et al.[27]

Possible mechanisms through which phyto-estrogens and mammalian lignans may exert a protective or inhibitory influence on prostatic neoplasia include both direct and indirect pathways. Phyto-estrogens inhibit the growth of both androgen-dependent and androgen-independent cancer cells in vitro[24], and could conceivably exert an inhibitory effect on prostate cancer either by directly lowering testosterone levels or by down-regulating its proliferative and trophic effects on prostatic epithelial cells. The phyto-estrogen genistein is an inhibitor of several enzymes, including topoisomerase II[28], an enzyme believed to play an important role in cancer cell survival. Certain phyto-estrogens have also been shown to act as inhibitors of angiogenesis[30], the process of neovascular proliferation thought to be crucial for a small focus of neoplastic cells to receive the blood supply and nutrients required to grow to a clinically relevant size. Finally, both phyto-estrogens and lignans possess antioxidant activity[31] and may utilize this property to block carcinogenic alterations to prostatic cytostructural components mediated by toxic free radicals.

Conclusions

In summary, carcinoma of the prostate is a disease for which there is no known method of prevention and which inflicts an enormous toll on the Canadian male population in terms of morbidity and mortality. Beyond the very early stages of the disease, it has also managed to elude curative treatment, largely because of its refractory susceptibility to hormonal manipulation. Epidemiologic data suggest that environmental factors, such as diet, may account for the significant differences in the frequency of prostate cancer among various geographic regions. Although several studies have reported an association between fat consumption and prostate cancer, the lack of consensus among different investigators with respect to this issue has directed attention toward the therapeutic potential of other dietary components.

Recent studies suggest that two structurally-related classes of dietary compounds, phyto-estrogens and mammalian lignans, may play a protective role in prostate cancer. The plasma and urinary concentrations of these compounds in individual subjects appear to be inversely proportional to the population frequency of prostate cancer. Furthermore, separate in vitro studies have provided convincing evidence of the anti-carcinogenic properties of these substances. It appears likely, therefore, that dietary components may be capable of influencing the pathogenesis of prostate cancer, perhaps by preventing the progression from a "latent" asymptomatic form to one of clinically invasive disease. This phenomenon would be consistent with (a) the extremely common incidence of latent histological cancer in young men of essentially all regions of the world[32], and (b) high levels of phyto-estrogens in young Japanese children[33],

suggesting a life-long protective mechanism against malignant transformation of prostatic epithelial tissue. More work is needed to clarify the role of these and other dietary compounds in the natural course of prostate cancer. Such approaches toward clarifying the dilemma of prostate cancer are vitally important and will hopefully lead to more effective strategies of treatment and prevention of this disease.

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National Forum on Breast Cancer, Montreal, Quebec

Laura Hopkins, B.Sc., M.Sc. (9T5)

The National Forum on Breast Cancer was held in Montreal on November 13-16, 1993 to consolidate current knowledge about breast cancer and to establish a formal research agenda. This was the first forum which included the participation and cooperation of medical professionals, breast cancer survivors, government and media.

Dr. Marie-Dominique Beaulieu spoke about risk factors for breast cancer, stressing that they do not contribute much to the probability of developing breast cancer. She stated that 70% of women have no risk other than female gender and age. She outlined three categories of risk:

High Risk:

- Age >60
- Country of Birth: Industrialized countries are associated with increased risk due to the associated lifestyle.
- Cellular atypia & hyperplasia.

Intermediate Risk:

- Previous breast cancer
- First-degree relative (mother, sister, daughter) with breast cancer.
- Hyperplasia without atypia.

Low Risk:

- Low socioeconomic status
- Nulliparous
- Menarche < 12
- First pregnancy > 30
- Late menopause > 55 and obesity at menopause.

A number of contradictions and recommendations have been made in recent years regarding screening and prevention. Here's what was said at the conference:

Screening

Mammography:

- It is beneficial to screen women 50 to 69 every 2 years.
- For women age 35 to 49 there is no evidence of any benefit of screening. It is recommended only for those who have risk factors/suspicious masses and who desire screening.
- Under age 35 - never.

Clinical Breast Examination (CBE):

- No value without proper training of physicians. Some studies indicate CBE is a useful adjunct to screening mammography.

Breast Self Examination:

- Little evidence of value. Advocate starting in late teens to become familiar with 'normal' so that when and if there is an irregularity it will be recognized.
- Must ensure it is done correctly.

Prevention

- Diet: No proven risk associated with a high fat diet. Some evidence that a diet high in fruits and vegetables is associated with a decreased risk. Modest increased risk with alcohol consumption (1-2 drinks per day).
- Tamoxifen: No guidelines established regarding the value of Tamoxifen in decreasing the risk of breast cancer.
- Post-Menopausal Hormone Replacement: Modest relationship between long-term use of estrogen replacement therapy (ERT) and breast cancer. Surveillance study recommended.
- Environmental Contaminants: Limited data exists.
- Oral Contraceptives: Data does not apply to currently available contraceptives. Among older formulations, a relationship exists between OC use and breast cancer, especially when started early. Recommend pharmacy records be kept from now on for future studies.
- Simulation of Artificial Pregnancy: Addresses the protective effect of giving birth early (20 -24). Research currently being pursued - no data yet.
- Breast Implants: No increased cancer risk with silicone implants. No data regarding foam-covered implants.

- Prophylactic Mastectomy: Prevalence is unknown. Practice may increase as women are identified as being carriers of breast cancer 1 gene. The risk of breast cancer is not completely eliminated by mastectomy.

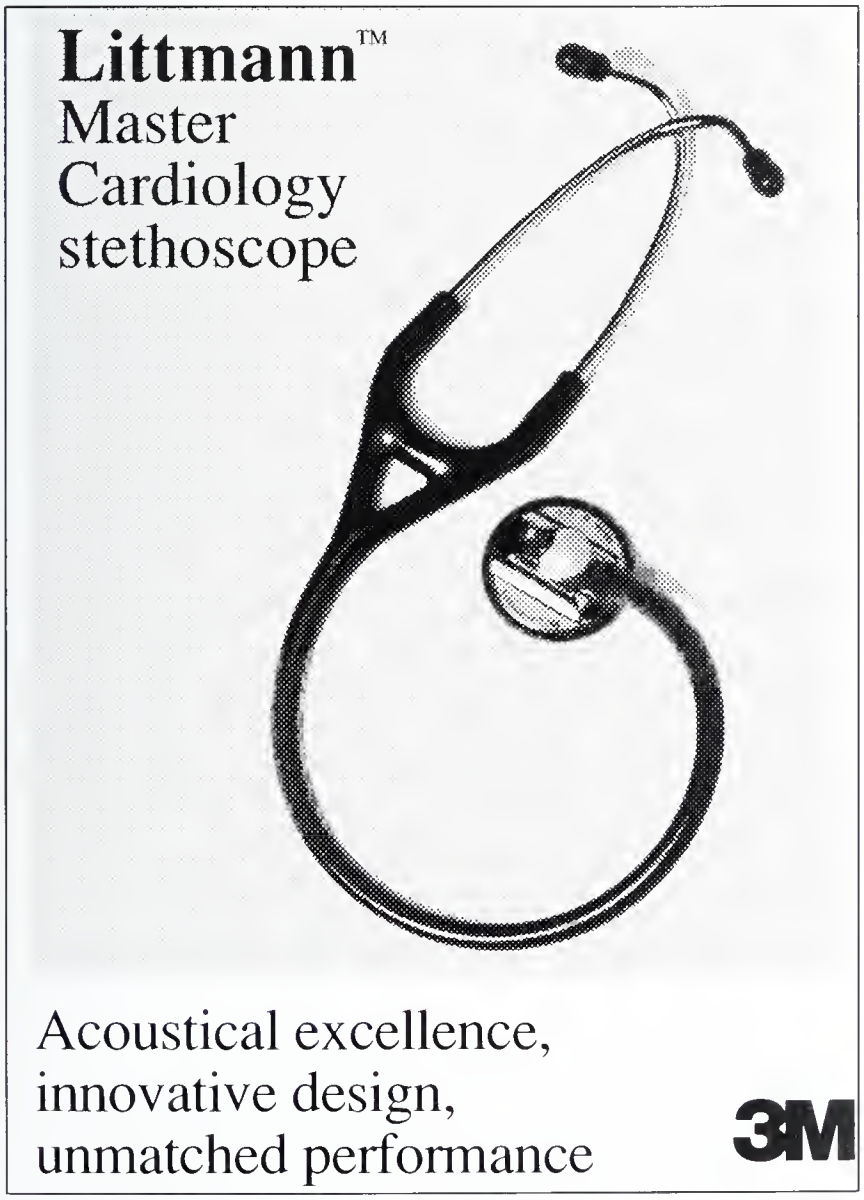
General Recommendations and Comments

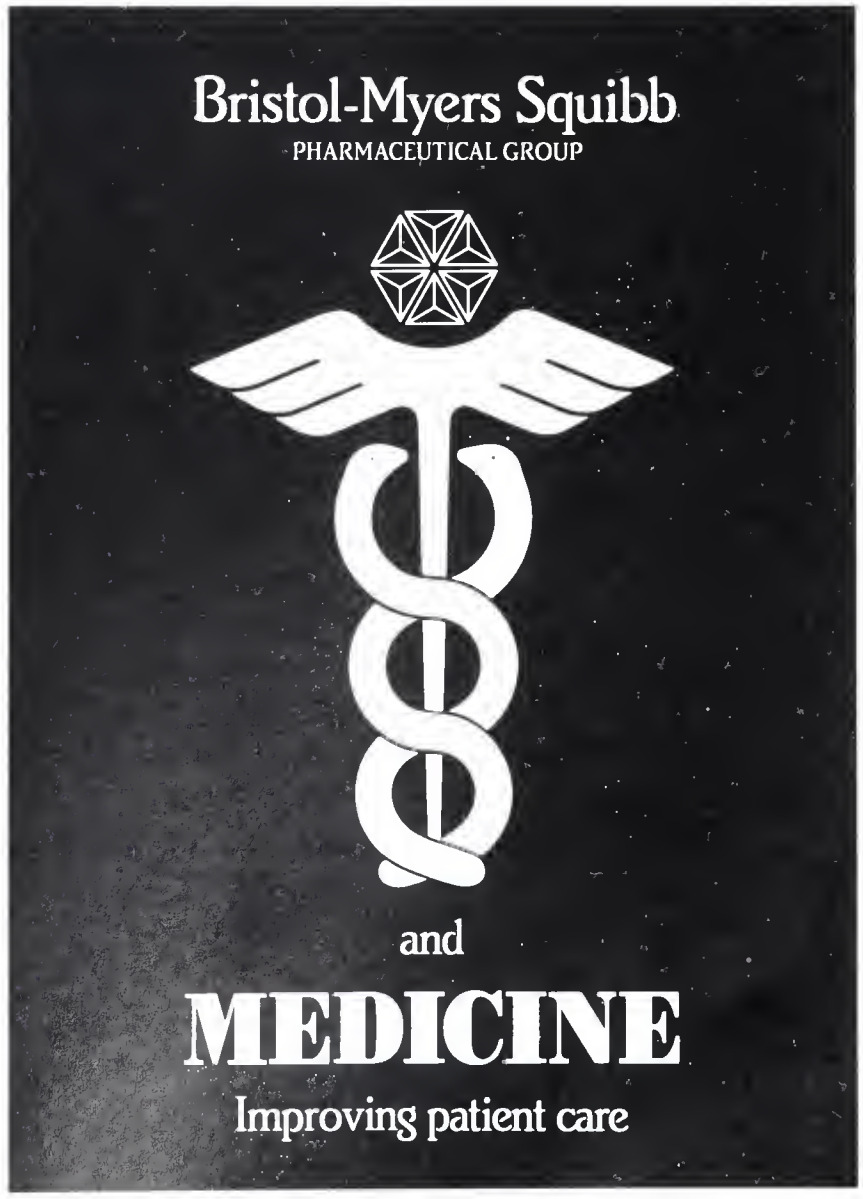
1) Mammography. For the over 50 group there is a 15 - 30% decrease in breast cancer mortality with screening. There is no statistical benefit of screening women under age 50 (actual benefit is 0-3% depending on which study is examined).

2) Only 33% of women know that increasing age is a risk factor for breast cancer and older women especially were less likely to know they were at risk. Women under age 50 feel a higher amount of vulnerability. There is a need to make the 50-69 year-old group aware of the benefit of screening mammography.

3) Rural and urban differences: Studies have shown that women who live in rural areas are less likely to have had and been offered screening mammography. There is a need to close this gap as soon as possible.

4) The incidence of breast cancer has increased in the last 10 years, the major impact being on women over age 60. Although mortality remains unchanged, there is no indication that therapies of recent years have improved survival.





Interview: Dr. Roy Clark

Cindy Grief, B.Sc. (9T5) and
Matthew Stanbrook, B.Sc. (9T5)

Dr. Roy Clark

Dr. Roy Clark is a radiation oncologist at The Ontario Cancer Institute/Princess Margaret Hospital and Professor of Radiation Oncology at The University of Toronto. He took part in the National Forum on Breast Cancer as Chair of the Scientific Committee. He shares his insights on breast cancer treatment and on the conference itself.

The National Forum on Breast Cancer came into being following a report by Barbara Greene M.P., Chair of the Sub-Committee on the Status of Women. The report, entitled "Breast Cancer: Unanswered Questions", was presented to The House of Commons in 1992. This report was part of a larger report by the Standing Committee on Health and Welfare, Social Affairs, Seniors, and The Status of Women, commissioned by the Federal Government in December, 1992. The government responded by agreeing to increase the funding for breast cancer by $20 million. An additional $5 million was set aside at that time. Half of this latter sum was directed to the establishment of a regional breast cancer information service across Canada, the purpose of which was to provide women with any information they needed regarding breast cancer in general. The remaining half was set aside to fund a national forum designed to gather together health professionals, patients, and any other lay people interested in breast cancer for the purpose of discussing where efforts should be directed in the upcoming years.

This marks the first time such a forum has been created. The object was to produce, by the end of the conference, a paper that would provide guidance to Health and Welfare Canada. Health and Welfare, in consultation with an organizing committee, chose to address the many problems to be discussed by setting up four working groups to deal with the broad areas of prevention and screening, research, treatment, and advocacy and support.

"The first treatment is the one that counts," he says. "Saving up treatment for the future, in case you recur, is not the way to go."

One of the problems mentioned at the conference was the disparity in the types of treatment that women receive at different centres. Dr. Clark acknowledges that a discrepancy exists in the proportion of patients receiving mastectomies compared with lumpectomies, whether or not radiation treatment is given, and the type, quantity, and duration of radiation therapy. He cites differences in physician training as the cause of this disparity. "It's not based on logic, but often on habit. It's just that this is what the people who trained (physicians) do, so they go on doing it. And it's based on habit." In addition, studies designed to examine the way radiation therapy is given have run into problems with standardization. "We did a study looking at patients who'd had a lumpectomy and had negative nodes. They were then randomized to breast radiation or no radiation, the idea being to see whether we could find a group of people who were at low risk of recurrence without radiation. When we looked at the number of different treatment methods, in eligible patients who did not enter the study, there were 40 different methods and some varied only slightly. There were variations (in treatment duration) between, say, 3 weeks and 5 weeks of treatment. So now there's another study which is comparing 5 weeks treatment with 3 weeks treatment that doesn't even use the fractionation that we had in our study."

When asked whether he believes the waiting lists for radiation therapy are going to change in the next little while, Dr. Clark is less than optimistic. "The waiting list is caused by a very large increase in the number of people who are having lumpectomies and with lumpectomies goes radiation. Even if the pathologist says the resection margins are clear, there's a 30% recurrence rate at the 5 year mark. If you do have radiation, it's 8%. There's a significant reduction by having radiation. The list could increase even more. "Faced with this situation, some patients are going to the United States for treatment, while others are being sent from Toronto to other Ontario centres as far as Thunder Bay. But Dr. Clark denies that anyone's care is being compromised. "In the study itself, which was an Ontario study, we have shown that there's no increased rate of recurrence in the breast if you delay the radiation by 1, 2, or 3 months after surgery. At the beginning of the study, we had set a period of 2 months (post-surgery) for eligibility, but we had to extend that to 3 months because we had so many patients who by the time they got to us for radiation were over 2 months anyway. There are many reasons why this happens. Sometimes it's due to delayed healing after surgery; people develop seromas or hematomas, or the necessity for complete metastatic workup. In looking at these patients, there were really no big differences in recurrence. So (waiting) at least up to 3 months is not detrimental to patients. Psychologically, maybe, but not medically."

Dr. Clark notes that it has been shown that a recurrence in the breast doesn't seem to impact seriously on survival unless it occurs at an early stage, implying that the doubling time of the tumour is so rapid that

metastatic disease likely already exists at the time the primary is initially treated. As a result, some investigators have suggested abandoning initial radiation treatment in these patients and simply treating recurrent disease as it appears with the result that a mastectomy may be required. Patients, however, have rejected this approach. "Almost unanimously they said, 'There's no way I want to go through any of this again. I want radiation.' As an analogy, take cancer of the alveolus in the mouth. You've had the tumour excised but the margins are a bit close. But we're not going to irradiate you. We can always wait and see if you do recur, and then do a hemimandibulectomy. I know (the analogy) is a bit extreme, but it's looking at it from the same angle, and nobody would go for that one. The only way to treat cancer is to aim for cure the first time around. It's more difficult after that."

Radiation therapy also has an important role in the palliative care of metastatic breast cancer. "It's a very effective pain reliever for bone disease. You can deal with pain very satisfactorily and patients will come back time and time again for further treatment to other sites. You can treat brain metastases palliatively. You can stop bleeding; radiation is hemostatic. You can shrink metastatic disease in the chest wall. It can be used to treat brachial plexus infiltration and spinal cord compression. Metastatic disease in the retina also responds to radiation."

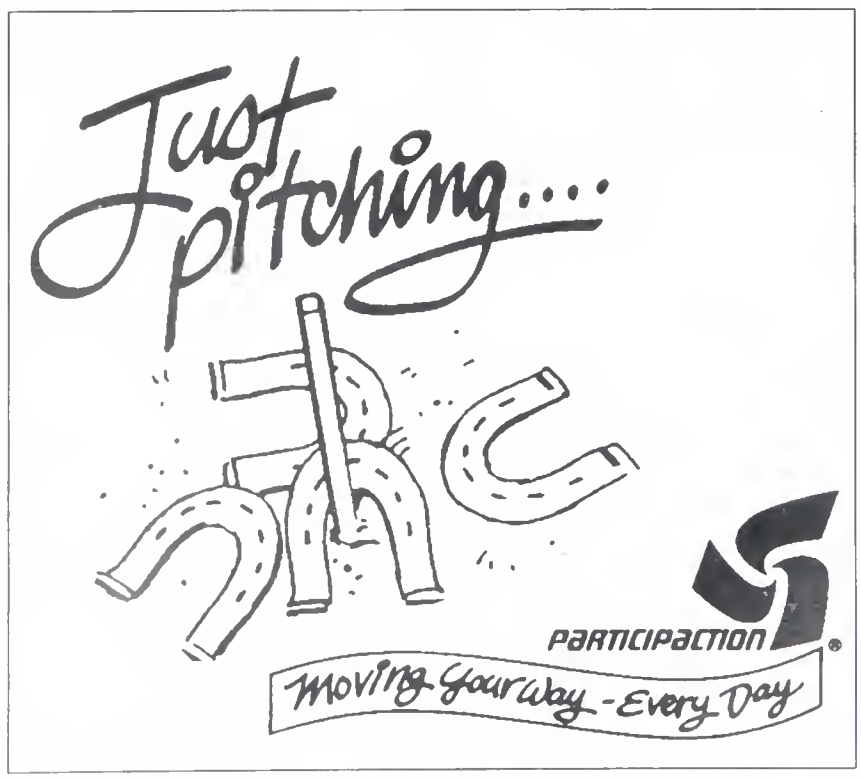
Other modalities of treatment for breast cancer have also come under a great deal of scrutiny. Dr. Clark agrees that many patients still have mastectomies needlessly. "The mastectomy rate varies tremendously: in Toronto, the lumpectomy rate (in place of mastectomy) is 80%, whereas in other areas the lumpectomy rate may be a low as 15-25% (with the remainder receiving mastectomy). But there may be some connection with accessibility to radiation."

The use of tamoxifen in breast cancer treatment has received a tremendous amount of public attention in recent years. Dr. Clark comments on a study currently underway to evaluate whether tamoxifen can be used to prevent development of breast cancer in women at high risk for the disease. "What they're doing is taking high risk patients and randomizing them between tamoxifen and placebo. (The study) came about because it was noted that people who were on tamoxifen in various trials had a lower incidence of second primaries in the opposite breast." He observes, however, that prophylactic tamoxifen therapy would not be without its problems. "Tamoxifen is not quite as innocuous as some people say. You can get depression, hot flashes, thrombosis, and irregular periods. You should not get pregnant if you're on tamoxifen. There is also a possibility of developing endometrial cancer. Patients with breast cancer (in whom tamoxifen is presently used) don't mind (the potential for adverse effects) because recurrence is far more serious than the risk of developing any of these other problems. But it's a different question when you're treating young, asymptomatic patients."

The National Forum on Breast Cancer itself attracted much interest in the United States as well as in Canada for its unique approach. Dr. Clark emphasizes the importance of this with respect to international networking, observing that the development of such networking has not been very successful in the past. As to whether more such conferences, bringing doctors and patients together, can be expected in the future, he states that efforts are being directed to continue what has been established by the National Forum. "We have to keep the momentum going. A lot of work went into this; everybody was exhausted because we did in six months what normally takes a year.

"This whole thing is being researched in detail. The Organizing Committee is meeting soon and will be meeting throughout the new year. The proceedings are going to be published and also important papers presented will be published in the Canadian Journal of Oncology. And there may be some mechanism by which the people who organized the Forum in the first place do meet again in the future from time to time because this has been quite a unifying force, right across the country. We have people from B.C. to P.E.I. In the past, it's been very difficult to get national studies together."

The conference was highly successful. Dr. Clark concludes that, "It not only enabled the medical professionals to hear more about the patient's ideas on the subject, but I think also survivors found out how much research is going on in breast cancer and, in particular, the problems that we have in dealing with cancer in general. I think they are beginning to understand that it's a very complex business."



The Use of Oral Contraceptives in Women Over Thirty-Five

Deborah Levy (9T5)

Hot flushes, mood swings, fatigue, irritability, irregular bleeding, and muscle and joint pains[1] are common complaints during the perimenopausal years, and thus it is understandable that this time can be very distressing to many women. While ovulation may be irregular and fertility declining, it remains important that women use an effective form of contraception during this period to avoid an unwanted pregnancy.

In the past, oral contraceptives were not prescribed to women over thirty-five years of age, regardless of their health status. It was felt that the cardiovascular risks outweighed the benefits of using "the pill". However, the data that these restrictions were based on is no longer relevant because the oral contraceptive pills that were used contained up to 80 µg of estrogen, significantly higher than the newer generation pills which contain 20 to 35 µg of estrogen.

In April 1993, the Health Protection Branch of Health and Welfare Canada revised the guidelines for the directions for use of estrogen-progestin combination oral contraceptives, noting that in "low-risk, non-smoking women of any age, the benefits of oral contraceptive use may outweigh the possible cardiovascular risks associated with low dose formulations"[2]. Absolute contraindications to oral contraceptive use include a history of thromboembolic disease, cerebrovascular or coronary artery disease, malignant tumors of the breast and endometrium, hepatic tumors, impaired liver function or a history of obstructive jaundice in pregnancy. Relative contraindications include uterine fibroids, migraine headaches, diabetes mellitus, hypertension, hyperlipidemia and varicose veins. It is suggested that the lowest dose of estrogen compatible with regular cycles[3] be used to decrease the risk of thrombosis and other estrogen related side effects. Thus, some women will be able to use the lowest dose 20 µg estrogen pill, but for others, a pill with 35 µg of estrogen may be necessary to avoid breakthrough bleeding and irregular cycles. Both formulations provide excellent contraception as well as other beneficial effects as noted below.

There exist several alternative methods of contraception for women over thirty-five years of age. Barrier methods such as condoms, the sponge, the diaphragm, or the cervical cap are effective when used correctly and consistently. The intrauterine device (IUD) is another option, but often causes heavy menstrual bleeding. Other women choose a more natural method, such as the rhythm method or withdrawal, although effectiveness varies greatly due to the unreliability of these methods. Sterilization is another effective form of contraception, though this method is not easily reversible. Although women can achieve effective contraception with any of these methods, they often require hormone replacement in the perimenopausal years as their ovarian function decreases and they begin to have symptoms[4].

It is well known that there are numerous benefits to taking oral contraceptive pills. For perimenopausal women, good cycle control and hormonal regulation decreases dysmenorrhea and menorrhagia, translating to a decreased incidence of iron deficiency anemia related to blood loss. The estrogen in the pills decreases hot flushes and mood swings, and also decreases the incidence of benign breast disease. Fewer functional ovarian cysts occur in women using oral contraceptives, although their occurrence is not eliminated[5]. Perhaps the more well-known benefits of the pill include a decrease in incidence of both ovarian and endometrial cancers by 40% to 50%. The incidence of ovarian cancer is directly related to the number of times a woman ovulates in her lifetime and thus is decreased while taking oral contraceptives which inhibit ovulation. As little as six months of use provides protection[6], and the longer the pill is used, the less likely ovarian cancer is to develop. Oral contraceptives' protective effect against endometrial cancer develops after at least one year of use. It is due to the progestins in the pills which inhibit proliferation of the endometrium and benefit women who may otherwise have anovulatory periods and endometrial hyperplasia[6,7]. This protective effect against both ovarian and endometrial cancer persists for at least 15 years after discontinuation of the pill. Other benefits of oral contraceptives include a decreased incidence of ectopic pregnancies, rheumatoid arthritis and an increase in bone density[7].

Serious side effects of oral contraceptives do exist, including hypercoagulability and venous thromboembolism (although these complications are more important in women who smoke), alterations in glucose metabolism, adverse alterations in the lipid profile, and hypertension (though risk is related to race, family history, obesity, diet, smoking and the duration of the use of the pill). Additionally, oral contraceptives have interactions with several medications, including anticoagulants, anticonvulsants, antidepressants and some antibiotics. Although in the past the pill was implicated to increase the risk of myocardial infarction, there is no evidence that newer formulations containing low doses of estrogen (less than 50 µg) are associated with an increased risk of cardiovascular disease[8]. The relative risk of cancer of the liver is increased about four times in women who have used an oral contraceptive for eight years, although the incidence of this neoplasm is estimated at only 3.4 per 100,000 women using oral contraceptives[8,9]. Controversial research has suggested an increased incidence of breast cancer in women who take the pill. However, if all of the studies are considered together, only a very small increase in risk may exist for

women who have used the pill for greater than 8 years, and this risk should not affect the prescription of oral contraceptives[3,6] .

Since a woman is now able to use oral contraceptives up until the time of menopause, it is useful to know when she has reached this stage. She may then be switched to hormone replacement therapy, which differs in pharmacological content, but continues to protect against the effects of declining levels of estrogen. To determine if menopause has occurred, the physician should obtain an FSH (follicle stimulating hormone) level on the sixth day the woman is not taking any pills[3] (or the sixth day of inert pills). Menopause is indicated by an elevated FSH level.

Today's generation of low-dose combined estrogen-progestin oral contraceptive pills are safe and beneficial for healthy, non-smoking women over the age of thirty-five. It appears that the benefits of the pill outweigh the risks of its usage and provide significant relief from numerous perimenopausal symptoms.

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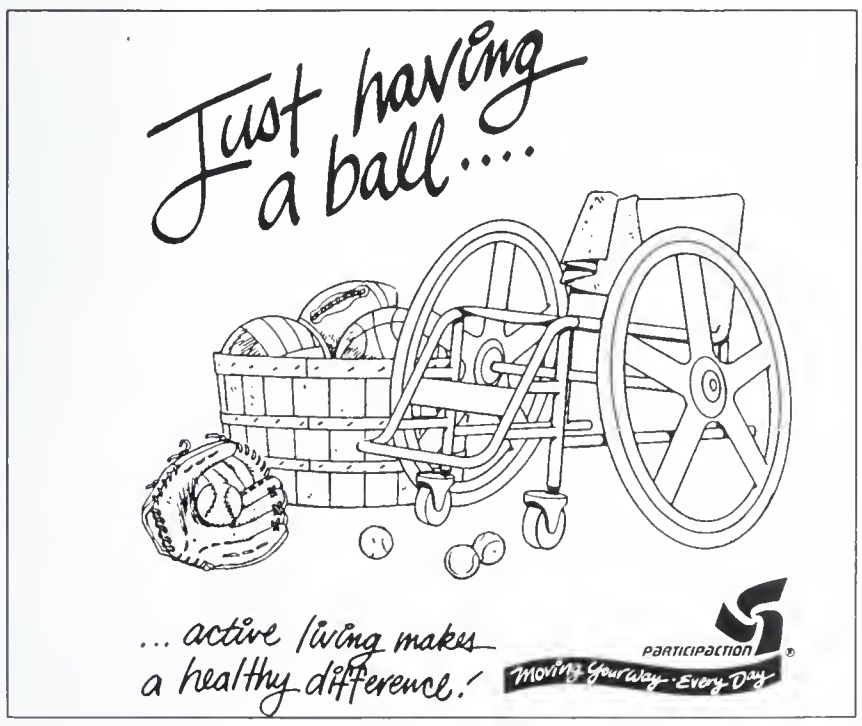


Medical Student Research Day

C.I. Whiteside, M.D., Ph.D., F.R.C.P. (C)

Associate Professor, Department of Medicine and
Co-Director, Annual Medical Student Research Day

Annual Medical Student Research Day 1993-94 was a great success thanks to the participants (102 Medical students, 5 Biomedical Communication students and 16 judges from the Faculty and senior postgraduate training programmes). For the first time, the Student Research Day was supported by a generous gift from Merck Frosst Inc. This funding enabled sponsorship of Professor Phil Gold, Chair, Department of Medicine, McGill University and production of an advertisement poster and abstract booklet of high professional quality.

Professor Gold opened Student Research Day with an enlightening talk entitled "The New Millennium: The Clinician-Scientist." Dr. Gold indicated that we are entering an era of scientific investigation in Canada where the M.D. and Ph.D. scientists must work together applying basic science discoveries to the understanding and treatment of human disease. He encouraged students participating in Research Day to continue their creative efforts in the realm of investigation. It was a great honour and pleasure to hear Professor Gold (M.D., Ph.D.) who exemplifies the role model of Canadian clinician-scientist.

On behalf of the Medical students, faculty, Michael Paré (Co-Director of Research Day) and myself, special thanks to Laura Hopkins and her Committee for the production of the remarkable abstract booklet. Laura also managed to present two excellent posters at Research Day and her overall contribution to the event was invaluable.

Behind the scenes management of Student Research Day by Diana Alli was not only very much appreciated, but was essential for its success. Also, thank you to the many students who helped assemble and disassemble the poster boards.

The response of the students and faculty indicates that research as part of medical student education is an extremely worthwhile endeavour. Although there is a competition for prizes, this is not the principal focus of Research Day. As one student mentioned to me, "I thought it was fantastic and I really enjoyed sharing my research with other students and faculty." Research Day is an opportunity for students to promote research experience among themselves. It is my hope that undergraduate medical students will continue to involve themselves in research and that faculty will continue to strongly support their efforts. There is no doubt in my mind that many of these students will be the academic leaders of tomorrow.

Presented here are the winning students and the titles of their posters:

Digital Multimedia Based Radiology Teaching File

Andreas von Ritschl

CYNTHIA YEE

Hemifield Pattern Electroretinograms in Normal Patients

Tony Wong

Efficient Trans-Cleavage of a Stem-Loop RNA Susbstrate by a Ribozyme Derived from Neurospora vs RNA

Hans Guo

Growth Factor and Nuclear Proto-Oncogene Induction of Human ß-Myosin Heavy Chain Transcription Requires a DNA Element Encompassing an AP-1 Binding Site

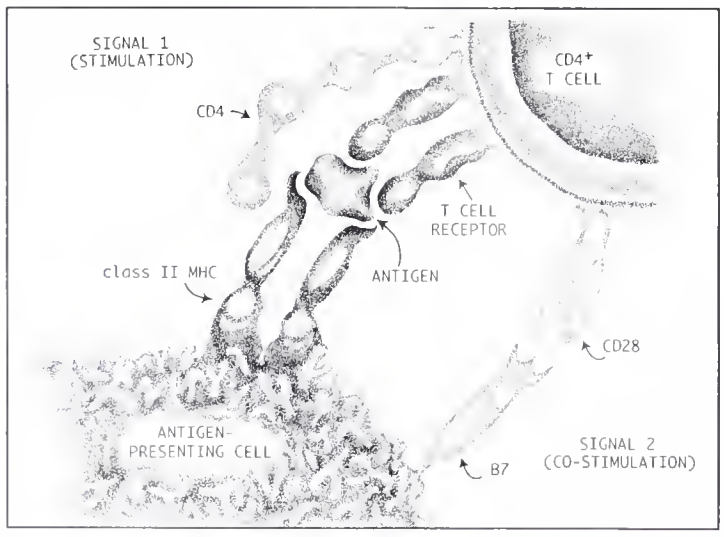
Michael Heffernan

Intracellular Membrane Permeant Ca^{2+} Chelating Buffers In Acute Spinal Cord Injury: A Preliminary Study

Demetrios Drakos

Thymic T Cell Anergy in Nod Mice is Reversed by Co-Stimulation Via CD28

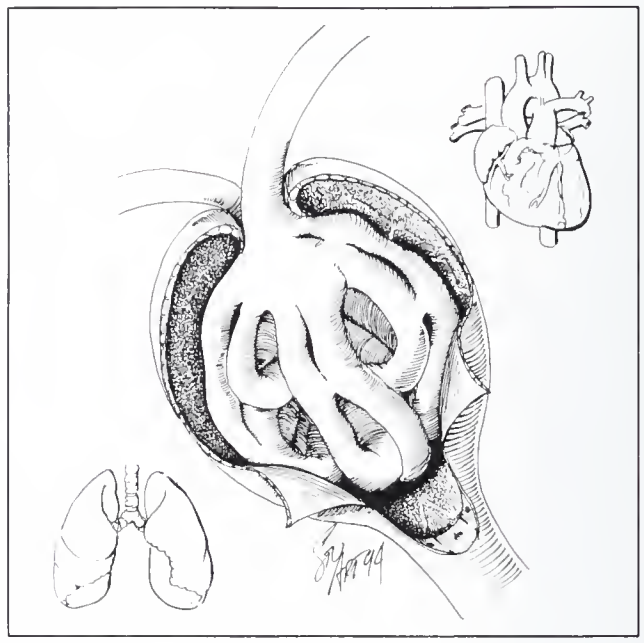
Kevin Laupland



MONICA WHALLEY

Sustained Vasoconstriction Associated with Daily Cyclosporine Dose in Heart and Lung Transplant Recipients

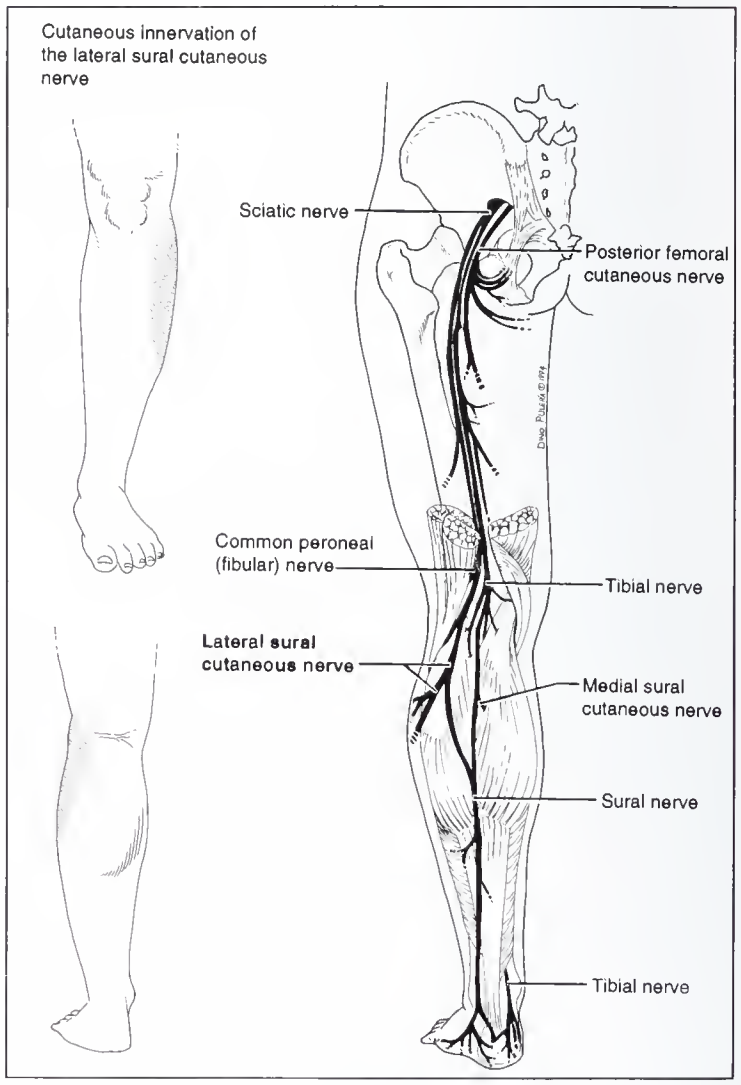
Christopher Chan



STUART McGINNESS

The Neurosome of the Lateral Sural Cutaneous Nerve of the Calf: Anatomy of the Innervated Fibula Osteocutaneous Flap

Lawrence Tong



DINO PULERA

Words of Advice from Dr. Robert Salter

Andrew Hyman, B.Sc. (9T5) and Fung Yeung (9T5)

Dr. Robert Salter

Dr. Robert B. Salter (4T7) is a world-renowned orthopaedic surgeon, teacher, and scientist. He is the creator of the innominate osteotomy, the Salter-Harris classification of epiphyseal plate injuries, his *Textbook of Disorders and Injuries of the Musculoskeletal System,* and the biological concepts of continuous passive motion (CPM) for joints. For over three decades, his contributions to surgery, teaching, and research have earned him numerous honours and awards, including a recent Doctor of Science *(honoris causa)* from the University of Toronto. This University Professor and Professor of Surgery (at U of T), senior orthopaedic surgeon at The Hospital for Sick Children (HSC), and Project Director of the Hospital's Research Institute, kindly shared his time with us as we discussed his views on life as a clinician scientist, research funding and our health care system.

When asked what role he feels research holds in a medical student's education, Dr. Salter explains that there are two distinct types of research which one can pursue: basic or clinical. Both are equally important and he strongly encourages students to investigate and experience both of these fascinating realms. He believes that through research one can seek answers to intelligent questions. He states, "When I was a student, there was little opportunity to be involved with research. Students never questioned authority, we never questioned dogma (that hadn't been proven scientifically), and we were given the impression that we were to learn what we were being taught and learn it verbatim. This is a very superficial way to look at education and I'm very pleased about the new curriculum which is based on problem solving and trying to stimulate bright young students to tackle a problem on the basis of general principles and academic research." Moreover, he believes that these skills will prove invaluable as one is constantly faced with problem solving situations with respect to patients, research, better ways of teaching and administration.

Many medical students look for an active learning experience in summer medical research but often get disappointed when they find themselves working as summer lab technicians, thus losing their interest for the field of research. Dr. Salter acknowledges this problem, which stems from a basic lack of funding. At times, he admits, it is hard for the supervisor to let the student pursue his or her own field of interest as the scientist's funds (obtained from a granting source) are strictly allocated to a certain area of research and additional ideas are left with little financial support. But despite these minor deterrents, one should not lose interest in research. It is in the senior years as a research fellow that one finally gains independence as an investigator. On a more personal level, he relates his own story of his first research experience in England. This project was funded by a grant he obtained on his own. Afterwards, he returned to join HSC as a clinician-scientist. As a research supervisor he strongly encourages his own research staff to think independently and pursue their goals. He states, "I always try to stimulate the people working with me to think in an original way and not just act as a pair of hands or as a lab technician. I try to teach students the 16 steps of a research project, which I have found useful over the years." The motivation for research can best be epitomized by what Voltaire called a "constructive discontent", meaning that one should not be content with the present state of knowledge. But Dr. Salter realizes that at times the path is not so easy; as Professor Perkins once said " The training of a doctor is such that it is difficult for him or her to break with tradition". There is an inherent tendency to accept tradition and not think in an original way.

In his keynote address to the graduating class of Uof T in 1993, Dr. Salter advised students "... not to follow the established path of clinical empiricism but rather, through research, to explore where there is no path and leave a trail that leads into the future." Regarding this statement, Dr. Salter explains that he is encouraging a frame of mind he feels students should strive to achieve. "Imagine something new...question dogma". He even invites students to question his teaching. After all, learning is a process that encompasses one's entire medical life and only through questioning can new knowledge be acquired.

When asked whether he has ever found it hard to challenge pre-existing ideas, Dr. Salter exclaims that for some of his original ideas he has faced considerable skepticism. One idea in particular was that of continuous passive motion. He originally conceived the idea from many observations including his own experiences as an athlete and the many injuries he sustained while at the University of Toronto. "I learned if I could stay away from an orthopaedic surgeon and not be put in a cast, I then did a lot better." Many of his teachers disagreed with this notion, their defence being that "...for centuries the medical profession has immobilized injured joints and surely not everyone is wrong." But

Dr. Salter refused to accept this and in 1970 he began working on CPM. To date all the studies have demonstrated the greater efficacy of this technique compared with immobilization.

Dr. Salter once claimed that "To be effective...the medical scientist must merit the respect of both fellow clinicians and fellow scientists and this calls for exemplary performance in both fields." He has excelled as a doctor, researcher, teacher, administrator and family man. When asked how he balances and maintains excellence in so many aspects of his life, Dr. Salter explains that first and foremost, all of these positions require a great amount of energy and commitment. He states that as an academic many things are expected. "One must be an exemplary physician and surgeon and this takes a lot of time and effort." Therefore, he makes the most of his time. "The quality of time is better than the quantity. One must have his or her priorities straight. It is difficult to be successful in all components, but if you give the best of yourself then you can make a worthwhile contribution in all areas. You must always keep your eye on the family life to make sure your family is not being neglected because of all these other activities."

Dr. Salter offers the following advice to the young clinician-scientist who is trying to balance the roles of being a doctor, researcher, teacher and administrator. He notes that these fields have all become increasingly sophisticated and demanding. During his earlier years in medicine, it was easier to find time to coordinate multiple roles and maintain excellence in each. Thus he advises the young doctor who chooses academic medicine to strive toward being an exemplary physician and then invest effort in one or two of the other activities, namely, research, teaching, or administration.

Dr. Salter adds that he is optimistic about the current state of the medical field in Canada. He says that despite the limited funding which has stressed the health care system, "we have learned from the hard times to work more effectively", and he cites shorter hospital stays and "same-day surgery" as examples. Although compensation for doctors may not be optimal, Dr. Salter shares his philosophy on practising medicine. He reminds us that being a physician is a privilege: "to be in a wonderful profession, to be in a free country, to have had great teachers...and to have received all those benefits through no credit to ourselves." After having enjoyed the tremendous privilege of studying medicine, there is an inherent duty to give something back in return, whether it be through patient care, research, teaching or administration.

Despite the cutbacks in the financial support of research, there is still good opportunity for people to pursue high quality research in Canada. Dr. Salter acknowledges that tight funding has increased the competition for research grants and that the assessment of research projects by the peer review system is more critical than ever. In general, the first research grant is the most difficult one to acquire. Hence he suggests that initial applicants consult senior scientists for their experience and advice.

Comparing Canada with other countries, Dr. Salter believes that Canadian medical schools are among the best, noting that the teaching of medicine in Canada is more regulated than in many other parts of the world. He would like to see a larger percentage of the GNP allocated for research funding, noting that the government must become better educated regarding the importance of research before such progress can be made.

Aside from a year in England, Dr. Salter has based his career in Canada. Despite offers from prestigious institutions such as Harvard and Oxford, Dr. Salter has remained in Toronto. He explains that "as a sixth generation Canadian, Canada has been very good to me, and that I would like to give something back to this country as a Canadian." He is pleased that all Canadians are covered for health care and are thus protected from financial destruction after the misfortune of a catastrophic illness or injury. And so there are many good reasons why he would never leave Canada.

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Nicaragua: War and its Aftermath

Lori Hasulo, B.Sc. (9T5)

"La vida es dura" - life is hard for Nicaragua's four million people. Nicaragua has often been described, in the popular press, as the poorest country in the Western world, after Haiti. This summer the International Health Program allowed me to spend three months learning and working in Managua, the nation's capital.

I was interested in venturing to Nicaragua for a number of reasons. I had previously visited Mexico's interior on a tour designed to explore the political and sociological roots of poverty in developing countries in Latin America. In addition, I was eager to see how medicine was practiced in a country other than Canada and to have the opportunity to learn a new language.

In order to begin to understand what it is like to live in Nicaragua, it is necessary to have an historical perspective. The indigenous population and culture were destroyed shortly after Christopher Columbus's arrival in 1502. The social stratification established then changed little over the ensuing 500 years. In 1979 , after 45 years of dictatorship under the U.S.-supported Somoza family, Nicaraguans succeeded in taking back control of their own country in a popular revolution. The Sandinista party, named after its founder Augusto Sandino, tried to rebuild the country after Somoza fled with most of the nation's money. It was not easy. At the time of the victory, there were 40,000 people dead, 200,000 homeless, 40,000 orphaned, 750,000 without food, 1 million refugees, and an external debt of $1.6 billion. Seventy percent of the people were illiterate and were not receiving medical attention, and 1 out of every 5 children died before the age of 4 years.

The Sandinistas set about improving living conditions and achieved a fair degree of success in a short time. However, in the early 1980s the United States was also beginning to fund the "Contras" in a war against the Sandinistas. As a direct result, throughout the eighties, the Nicaraguan government was forced to spend more and more money on defence and many of the social programs they had initiated began to fall apart. With the country bankrupt at the end of the war in 1988, elections were called and eventually the rival UNO party took power in 1990. U.S. aid, promised at that time, has still, at this writing, not arrived in Nicaragua. The country's economy remains devastated.

Armed conflict is not the only problem that Nicaragua has had to face in the past couple of decades. In 1972, an earthquake hit Managua and left 10,000 dead and 20,000 seriously injured. Most of the hospitals were destroyed in the quake. In 1988, hurricane Joan wreaked havoc on the east coast. Periodic floods and drought, coupled with the U.S.-sponsored embargo throughout the eighties, contributed to exacerbate the social and economic crisis.

It comes then as no surprise that the quality of health care in Nicaragua is steadily deteriorating. Medical equipment and medications are in short supply and the Ministry of Health can only account for 30 cents of each dollar originally marked for health care. My supervisor, Dr. Antonio Jarquin, and his colleagues have recently completed a study on the effects of the "Contra" war on economic and social development in Nicaragua. The vast amount of money that was needed to finance the war and the subsequent refusal of the U.S. to send the promised aid have destroyed many of the improvements made in health care achieved during the early years of Sandinista rule. Since the war ended, there have been increases in infant mortality, childhood diseases, malnutrition and illiteracy. Only 20% of the population has stable employment and a majority of people live below the poverty line.

Nicaragua has also witnessed an overall decrease in the number of physicians serving the population. Physicians working in the public hospitals receive very poor wages. As a result, many of them have a private practice in addition to their hospital duties. Dr. Jarquin quit his hospital job only a few years ago and was doing very well in his private practice. Now, however, many of his patients have lost their jobs and no longer have enough money to retain him as a private obstetrician. He currently works an average of 5-10 hours per week, whenever a patient calls for an appointment or has a baby. His wife, a psychologist, sees about the same number of clients weekly. The Jarquins have two children. They own a coffee farm, but because world coffee prices are so low, they are actually losing money on the farm. They are basically surviving from week to week, occasionally borrowing money from a mortgage on the farm. The Jarquins are doing relatively well financially compared to many of their friends.

Life in economic and social upheaval is "normal" for Nicaraguans. A 1988 study by a group of psychiatrists and psychologists concluded that 26% of the population in selected regions required psychiatric follow-up as a consequence of the war. Very little work has been done in Nicaragua in the area of Post-Traumatic Stress Disorder. One psychiatrist explained to me that since nearly 50% of Nicaraguans are 15 years of age or less, a majority of them have lived their entire lives under conditions of civil and military strife. This, therefore, is "normal" life. There are a number of organizations which have been set up to improve child health, promote human rights and assist those who have been injured in the war. These organizations confront funding problems as well as apathy from many Nicaraguans who have lost hope that changes can be made in their lives and in their country.

Towards the latter part of this summer, attacks by "rearmadas" - a group of ex-Sandinistas and ex-Contras, now joined together by a mutual dislike of the current political situation - on cities in the North of the country served as a poignant and all-too-scary reminder of the violence bred of economic necessity and a struggle for survival by a tired people.

The war in Nicaragua continues. Only the weapons have changed. Instead of guns and bombs, an economic stranglehold and international apathy continue to hold the country hostage. As for me, I open the newspaper each morning hoping not to find any news about Nicaragua, as in general, no news is good news. I plan to continue to educate myself about life in Latin America, and hopefully to return one day to a more peaceful Nicaragua.

Listening to Prozac: A Psychiatrist Explores Antidepressant Drugs and the Remaking of Self

Peter D. Kramer, 409 pp, $29.99, New York, Viking, 1993.

Listening to Prozac is an interesting collection of case studies, reflections and speculations on the use of antidepressants, specifically Prozac, in the twentieth century. Few drugs have captured as much public interest or attention from the medical community as fluoxetine hydrochloride, Prozac. Prozac, the first of the serotonin reuptake inhibitors, is said to have fewer side effects and a wider spectrum of use than the traditional antidepressants. Much of the media craze and public interest have not, however, focussed on Prozac's ability to treat depression, rather its reported ability to make the well "better than well". This phenomenon was coined "cosmetic psychopharmacology" by its first observer, the author of this book, Dr. Peter Kramer.

Dr. Kramer describes a phenomenon he calls "listening to Prozac". Through his conversations with individuals "transformed" by Prozac, Dr. Kramer comes to see character as inborn and biologically determined. Traits ranging from shyness and low self-esteem to compulsiveness are assumed to be biological, even genetic, as Prozac is effective in treating them. Prozac is described as transforming the shy and inhibited to assertive and flexible.

The first patient who drew Kramer's attention to the potential applications of Prozac was a woman named Tess. Tess was the eldest of ten children born to a depressed mother and an alcoholic father. Tess raised her siblings and became a successful professional. In her personal life, however, Tess would become involved in abusive relationships and suffered from low self-esteem. When prescribed imipramine, a tricyclic antidepressant, Tess's depression remitted and she told Dr. Kramer, "I am myself again." Despite her self-reported improvement, Kramer later prescribed Prozac as he felt Tess may still have "soft signs" of depression. On Prozac Tess was a transformed person. She was assertive, confident, less serious and did not enter destructive relationships. When off medication Tess then declared, "I am not myself." Dr. Kramer was then faced with the dilemma, "Ought I to provide medication to someone who was not depressed. . . I would be medicating Tess's chronic condition . . . sensitivity to conflict, residual damage to self-esteem - all odd indications for medication." Despite these reservations, Kramer did not hesitate to write the prescription.

Kramer offers a simple explanation for Tess's response to Prozac. He states that if Tess's social and psychological difficulties respond to a biological treatment, they must have been biologically encoded. All of human character, experience and suffering is assumed to physiologically encoded in serotoninergic pathways. Prozac for Dr. Kramer, is a drug not only for depression but for a host of other problems which are clearly not diagnosable mental illnesses. He believes we are entering an era where medications can be used to treat subclinical distress or even to enhance the functioning of the normal mind.

Listening to Prozac presents an interesting and radical understanding of the human condition. The fascinating stories of Kramer's patients are interspersed amongst anecdotes and research from the history of psychology and psychopharmacology, animal ethology, literature and philosophy. The book is written in a colourful and accessible style. Just as Prozac transformed the personalities of his patients, Dr. Kramer attempts to transform the traditional understanding of wellness, suffering and therapy. Although Kramer addresses some of the concerns with his model, he dismisses most of them by referring to the positive changes witnessed by himself and reported by his patients and thereby fails to adequately concern himself with some of the more disturbing inferences suggested by his analysis. Indeed, Kramer appropriately questions his own treatment by contemplating, "it is one thing for a doctor to be able to transform a patient with medication, quite another for the doctor to be able to sculpt the patient's personality, trait by trait." An individual experiencing difficulties no longer requires insight or an understanding of their suffering, rather it is a drug which is required. When Tess exclaimed, "I am not myself" when she was taken off Prozac, one is left questioning the value of a therapy which disappears once it is eliminated from the body.

Listening to Prozac is unquestionably a new and controversial view of psychiatry in what Kramer describes as the "psychopharmacologic era." Kramer's book is thought provoking, challenging and raises many of the dilemmas of modern psychiatry. The reader must however, listen to Kramer's tales of Prozac transformation, with more skepticism and critical thought than perhaps Kramer used while "listening to Prozac".

Amy Freedman , B.Sc . (9T5)

J.C. Boileau Grant - Anatomist Extraordinary

Clayton L. N. Robinson, 157 pp,
Fitzhenry & Whiteside Publishers, 1993.

This is a biographical sketch of the late J.C. Boileau Grant as depicted by Dr. Clayton L.N. Robinson and published by the Canadian publisher Fitzhenry & Whiteside.

Dr. Grant's life is outlined from his early years in Edinburgh through to his years as professor of anatomy at the University of Manitoba, the University of Toronto, and finally at UCLA. The book explores J.C.B. Grant's family relations, as well as his academic pursuits. The contribution Dr. Grant made to the study of anatomy, before his passing in 1973, is examined. Dr. Clayton's research into the life of J.C.B. Grant is extensive. He includes many interesting recollections, as retold by a variety of individuals whose lives where touched by Dr. Grant.

C.H. Sawyer, a colleague of Dr. Grant's at UCLA, recalls an incident where two women were looking at a skeleton of a young infant in a corridor exhibit, when Dr. Grant walked by with a student. In a voice loud enough for the women to hear, Dr. Grant remarked that the skeleton was that of George Washington as a baby. One of the women was heard to comment that they wondered why it was not at the Smithsonian.

A former University of Toronto student, W.D. Stevenson, remembers the outstanding anatomical drawings that Dr. Grant used to reproduce using only chalk and a blackboard. He also recalls the many kindly satires made of Dr. Grant's characteristic teaching ways, in University of Toronto's annual Daffydil productions. The spoofs were the student's way of expressing their admiration for such a great teacher. As it has been said in the past, imitation is the greatest form of flattery.

Grant has influenced the practices of many physicians through his teaching, either directly or from his publications. These publications include the popular Grant's Atlas of Anatomy, and the widely used A Method of Anatomy. Grant was an extraordinary teacher, as recognized by both his pupils and by those who have used his books as anatomy study aids. His contribution to the field of anatomy is also apparent in the anatomy museum that he helped develop at the University of Toronto.

The only flaw in this book is its tendency to progress in an illogical fashion at times, with the author leaping from one thought to another in a manner that is often hard to follow. However, this book is well worth reading, especially for those who have studied the human body with the help of Grant's Atlas of Anatomy.

Jayna Holroyd-Leduc, B.Sc., M.Sc. (9T6)

Helping Your Child Recover from Sexual Abuse

Caren Adams, M.A., and Jennifer Fay, M.A. 157 pp, 1992. Available from University of Toronto Press.

This book is a valuable resource for students, physicians and parents dealing with a sexually abused child. In particular, it is aimed as a guide for parents to help them cope with the day-to-day challenges they face through the course of their child's recovery. The authors, Caren Adams and Jennifer Fay, have written three other books aimed at lessening the impact of sexual violence. Caren Adams began in 1973 to assist sexual assault victims and their families, and to explore ways to prevent rape and sexual abuse. Jennifer Fay has specialized in sexual assault prevention since 1979, when she wrote He Told Me Not to Tell, one of the first booklets encouraging parents to talk to their children about sexual assault. Both authors draw on years of experience as crisis counsellors and have been active in the creation of programs for social change.

Helping Your Child Recover From Sexual Abuse is unique in that information for the parent appears on the left-hand page, and what might be said to the child, or activities for parent and child, appear on the right-hand page. The parent's information addresses more than the needs and concerns of the child. It provides healthy, practical advice for adults dealing with their own reactions to the abuse, and to the subsequent changes in behaviour they may notice in their child. A substantial number of issues are covered, including what immediate action to take, legal considerations, the responses of family and friends, the child's reactions to everyday life, grieving, rebuilding self-esteem, and dealing with confusion about sexuality.

One of the stronger aspects of this book is its ability to bridge the communication gap which can exist between parent and child. The parent may not realize that the child is in need of reassurance, or know how to provide it. For example, when a child reveals abuse during a divorce or custody battle, his or her disclosure may be viewed with suspicion. In this scenario the authors suggest that the parent might say: "Because your dad (mom) and I are fighting each other right now, some people may be suspicious of what you say. I am not. I know you don't have any reason to lie. I know this is embarrassing and unpleasant. It must have been hard to tell anyone." Similarly, the authors also provide guidance in how to deal with sensitive behavioural problems such as angry outbursts, excessive clinging or inappropriate sexual behaviour.

Although Adams and Fay do not refer to children of any particular age group, it is quite apparent that their book is targeted at the younger child. Issues pertaining to abuse occurring at the onset of adolescence or thereafter have been entirely ignored. Even for those children that were abused at a very young age, there is little on how to counsel them as they mature. The book only deals with concerns that can come up three months, six months, or up to a year after the abuse. After this period, an alternate resource must be consulted.

Overall, Helping Your Child Recover From Sexual Abuse is a practical and easy to read book. It provides concise, relevant information to parents on how to communicate with their child, and how to deal with his or her immediate emotional needs. It is an excellent resource for physicians both to read themselves and to recommend to their patients caring for a sexually abused child.

Ritu Sethi (9T5)

Cases in Chest Radiology

Angela Luong (9T6)

CASE 1

A 37 year-old HIV-positive man with a two-week history of fever, weight loss, and general malaise presented with acute onset of severe dyspnea. A week ago, he noticed some shortness of breath and a dry hacking cough. Physical examination revealed decreased air entry over the left lung field compared to the right side. A chest radiograph (Figure 1) was obtained. From the radiograph, what is the diagnosis?

Figure 1

ANSWER TO CASE 1

In the context of the clinical history and presenting symptoms, one should entertain *Pneumocystis carinii* pneumonia (PCP) amongst the differential diagnoses. *Pneumocystis carinii* is a microorganism of undifferentiated taxonomy; for many years it was classified as a protozoan until recent studies suggested that it may be more appropriate to consider it as a fungus. Although it had long been recognized to be a cause of pneumonia in immunocompromised patients, it generated enormous interest when, early in the acquired immunodeficiency syndrome (AIDS) epidemic, PCP was reported in 75% of AIDS patients. As a result of prophylaxis, PCP is no longer the most common complication in AIDS patients.

Chest radiographs are useful tools to assist in the diagnosis of PCP pneumonia. In the early stages of disease, a mixed granulo-reticular pattern can be observed. As the disease progresses, one may see progression of airspace consolidation, classically in a perihilar distribution. In the terminal stages of disease, consolidation will have increased to a point of almost complete airlessness. The posteroanterior (PA) plain chest radiograph (Figure 1) shows bilateral diffuse airspace disease with cystic spaces consistent with bullae or pneumatocoeles. In addition, a spontaneous pneumothorax is seen in the left lung. Spontaneous pneumothorax results from rupture of a pneumatocoele and occurs most commonly in the lung apices. Pneumatocoeles and pneumothorax are seen as complications of PCP pneumonia in anywhere from 10-40% of patients.

CASE 2

A 57 year-old previously healthy man complained to his family physician of diplopia while reading. According to his wife, his eyelids seem to droop as he read. He also noted generalized weakness and easy fatiguability exacerbated by activity that had been present for over several months. Recently he noticed difficulty swallowing solid foods. His family physician ordered a chest radiograph (Figures 2a and 2b) as part of the work-up. After viewing the chest radiograph the radiologist suggested a CT scan of the thorax to evaluate the patient further (Figure 2c).

ANSWER TO CASE 2

The chest radiographs (Figures 2a and 2b) reveal a well-lobulated mass measuring about 5 cm in diameter in the left anterior superior mediastinum. CT (computed tomography) imaging is needed to characterize this mass further.

Presented with such a history and given the anatomical location of the mass on imaging, a thymoma is the most likely diagnosis. The patient's complaints are consistent with myasthenia gravis, an autoimmune neuromuscular

disease resulting from autoantibodies that damage receptors for the neurotransmitter acetylcholine in the post-synaptic membrane at the neuromuscular junction. As a consequence of this impedance of nerve impulse conduction across the neuromuscular junction, repeated muscle activity easily brings on fatigue. Myasthenia gravis is often associated with abnormality of the thymus gland: thymic lymphoid hyperplasia (over 50% of myasthenia gravis cases) or thymoma (10-15% of myasthenia gravis cases).

A thymoma is a neoplasm consisting of thymic epithelium that can behave in a benign or malignant fashion. Often seen on imaging at the level where the great vessels branch off from the heart, thymomas may extend and displace these aforementioned structures posteriorly. Although myasthenia gravis is the most common disease associated with thymomas, other autoimmune disorders may be associated with thymomas or thymic hyperplasia including hypogammaglobulinemia, systemic lupus erythematosus, Graves' disease, inflammatory bowel disease (Crohn's disease and ulcerative colitis), pernicious anemia, Sjögren's syndrome, pemphigus vulgaris, and alopecia areata, as well as red cell hyperplasia.

On imaging, a thymoma usually presents as a well-lobulated round or oval mediastinal mass that may have calcifications at the periphery or throughout (not seen on Figures 2a and 2b). CT scanning is the imaging tool of choice in the investigation of patients with myasthenia gravis. Magnetic resonance imaging (MRI), although rarely used in Canada to investigate for thymomas, is also ideal and has become the imaging modality of choice in the United States.

Figure 2a

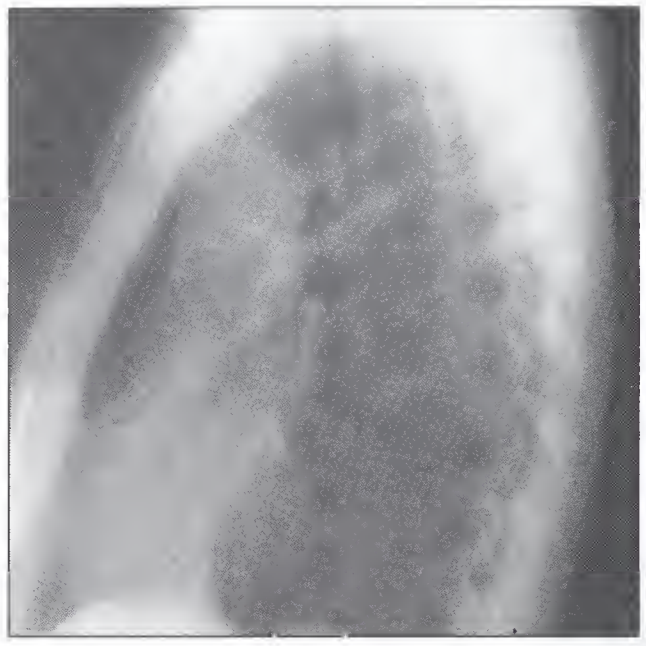


Figure 2b

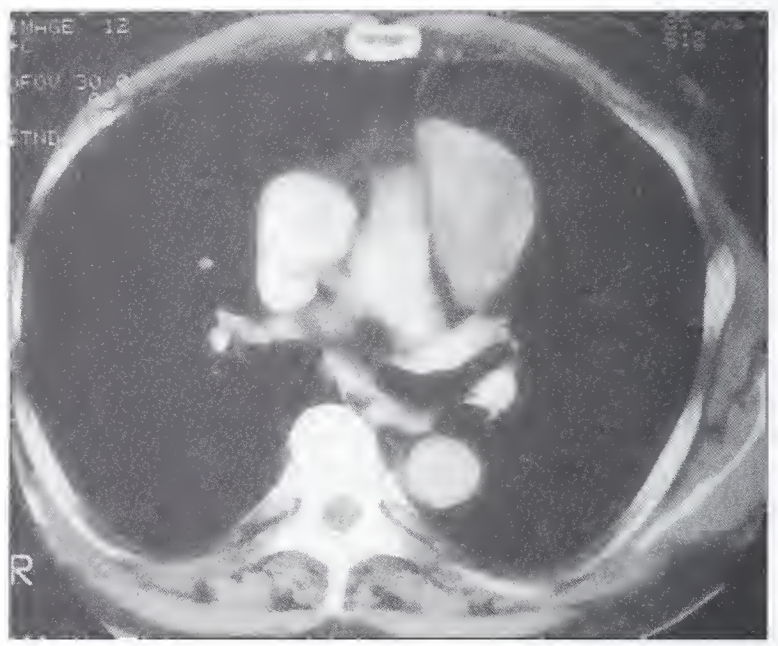


Figure 2c

CASE 3

A 40 year-old woman with a history of poorly controlled hypertension presented to the emergency room with severe "tearing" chest pain. She felt faint in the emergency room. Vital signs were: heart rate 110/min, blood pressure 135/95, respirations 18/min. In addition to the routine blood work, cardiac enzymes, an ECG, and chest radiograph (Figure 3a) were ordered. Subsequently a contrast-enhanced CT scan (Figure 3b) was performed.

ANSWER TO CASE 3

This is a classic presentation of a dissecting thoracic aortic aneurysm, as suggested by the history of hypertension and the signs and symptoms. It is later confirmed by the imaging studies. However, since severe chest pain is the presenting symptom, the primary goal of the imaging studies, ECG, blood work and cardiac enzymes

is to differentiate acute aortic dissection from acute myocardial infarction.

The chest radiograph (Figure 3a) shows bilateral pleural effusions manifested as blunting of the costophrenic angles bilaterally, but is not diagnostic of aortic dissection. There is also widening of the upper mediastinum.

Contrast-enhanced CT scan is required for accurate diagnosis. The CT scan (Figure 3b) shows an aorta with two lumens: the true lumen, and a false lumen where the dissection has occurred and into which blood is filling. The viewing of multiple images over time will allow distinction between the true and false lumens since the latter will fill more slowly. In most instances the false lumen usually is posteromedial in location. The pleural effusion is also well seen on the CT image.

Aortic dissections can occur anywhere along the aorta but the thoracic aorta just distal to the origin of the left subclavian artery is the most common site. In a patient with a history of hypertension, there is usually some atherosclerosis as manifested here as an unfolding of the aortic knuckle.

Although plain film chest radiographs and CT scanning are common imaging modalities employed to make the diagnosis, other modalities that may be used include transesophageal echocardiography, MRI, and aortography.

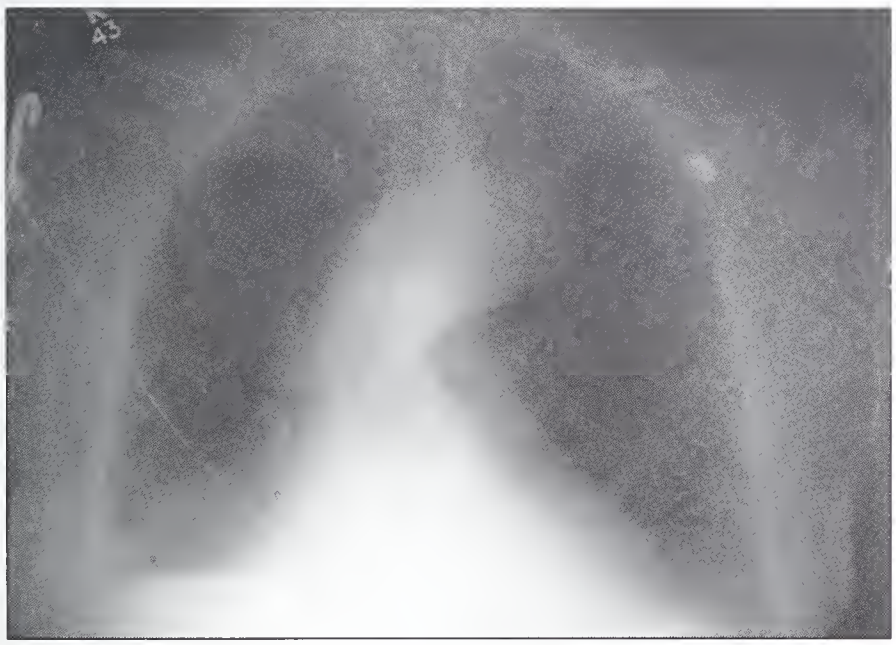
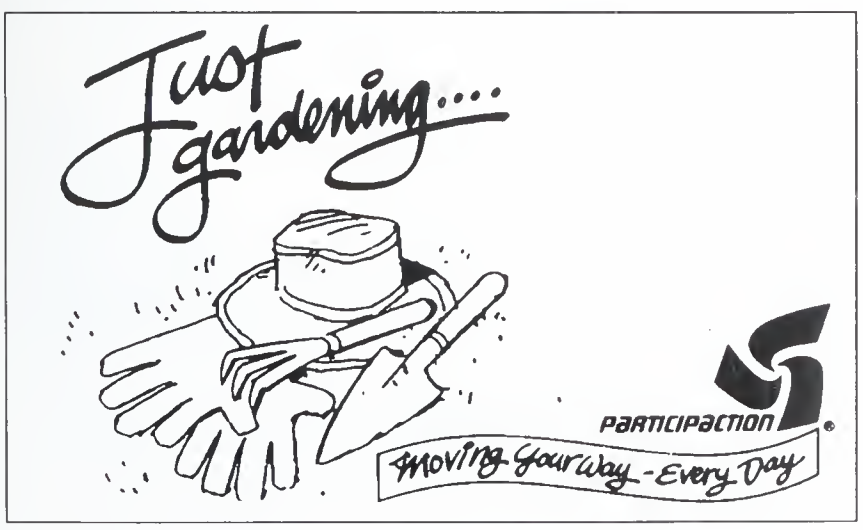


Figure 3a



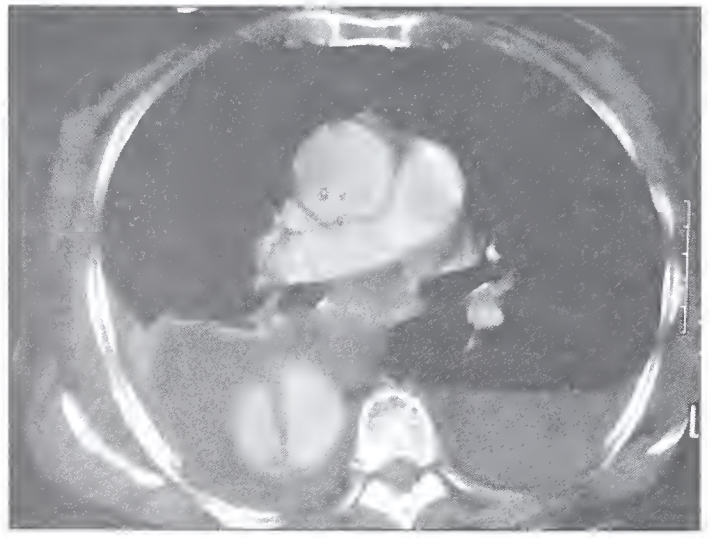


Figure 3b

CASE 4

A 43 year-old man presented with an eight-week history of low-grade fever, weight loss, fatigue, and loss of appetite. On several occasions he suffered night sweats. He is a recent immigrant from Malaysia. Physical examination produced unremarkable findings except for a few basilar crackles over the lung bases and some enlarged tender lymph nodes in the neck. Investigations performed included chest radiography and CT imaging (Figures 4a and 4b).

ANSWER TO CASE 4

The plain film image (Figure 4a) shows diffuse micronodular densities over the lungs. This pattern can be observed in sarcoidosis (often with hilar adenopathy), simple silicosis, miliary tuberculosis, extrinsic allergic alveolitis, or metastatic disease. However, given the clinical presentation and the small sized nodules (larger nodules being expected in silicosis), the correct diagnosis is disseminated or miliary tuberculosis.

From the plain film, a pattern of discrete, softly marginated opacities approximately 2 mm in diameter can be observed uniformly scattered throughout the lungs. These miliary nodules represent the hematogenously disseminated tubercle bacilli of *Mycobacterium tuberculosis* with their associated granuloma formation. These opacities may coalesce with disease progression and may make recognition of a miliary pattern more difficult. Bilateral hilar adenopathy and lymphadenopathy in the neck are present in this patient. Further evaluation using high-resolution CT scan shows miliary nodules as distinct dots against the background of aerated lung (Figure 4b).

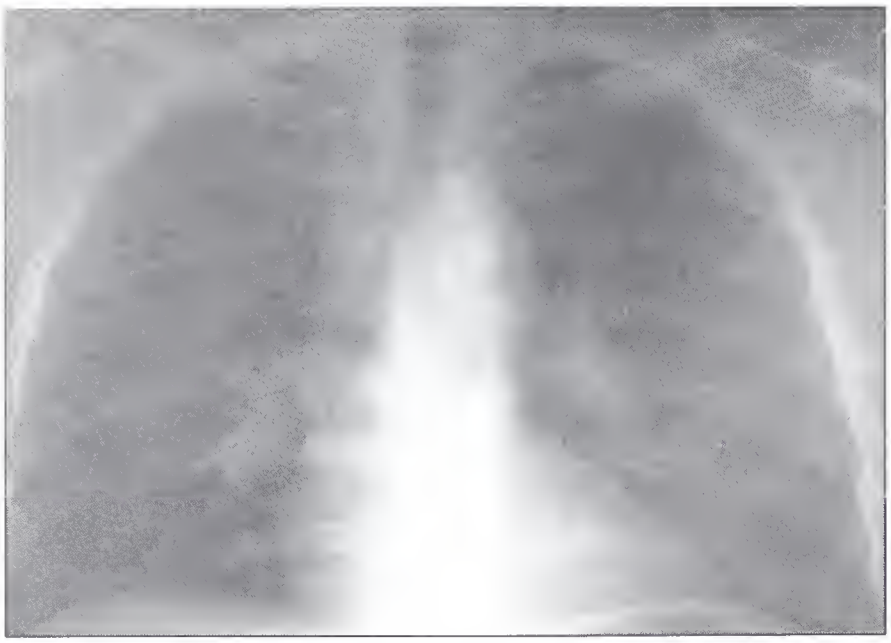


Figure 4a

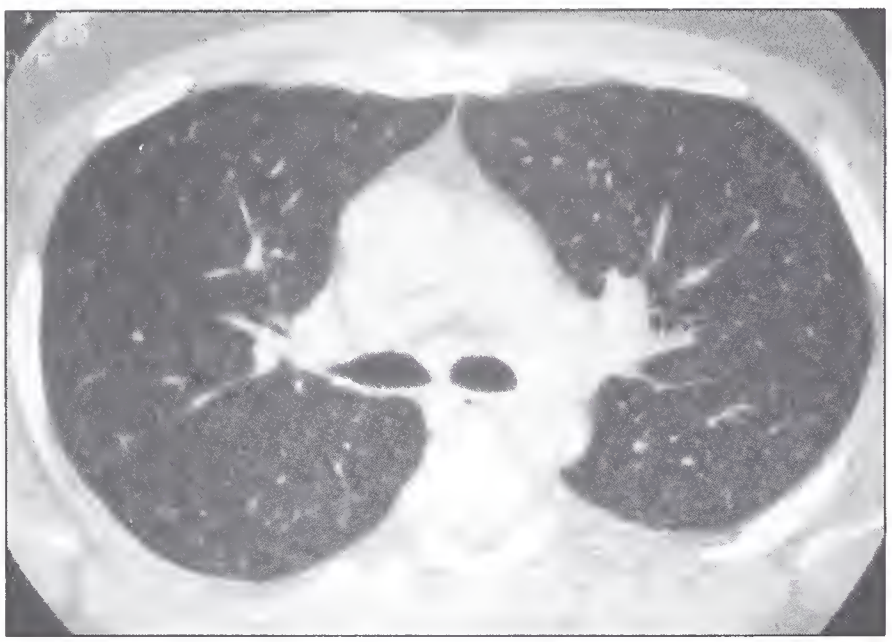


Figure 4b

Acknowledgements

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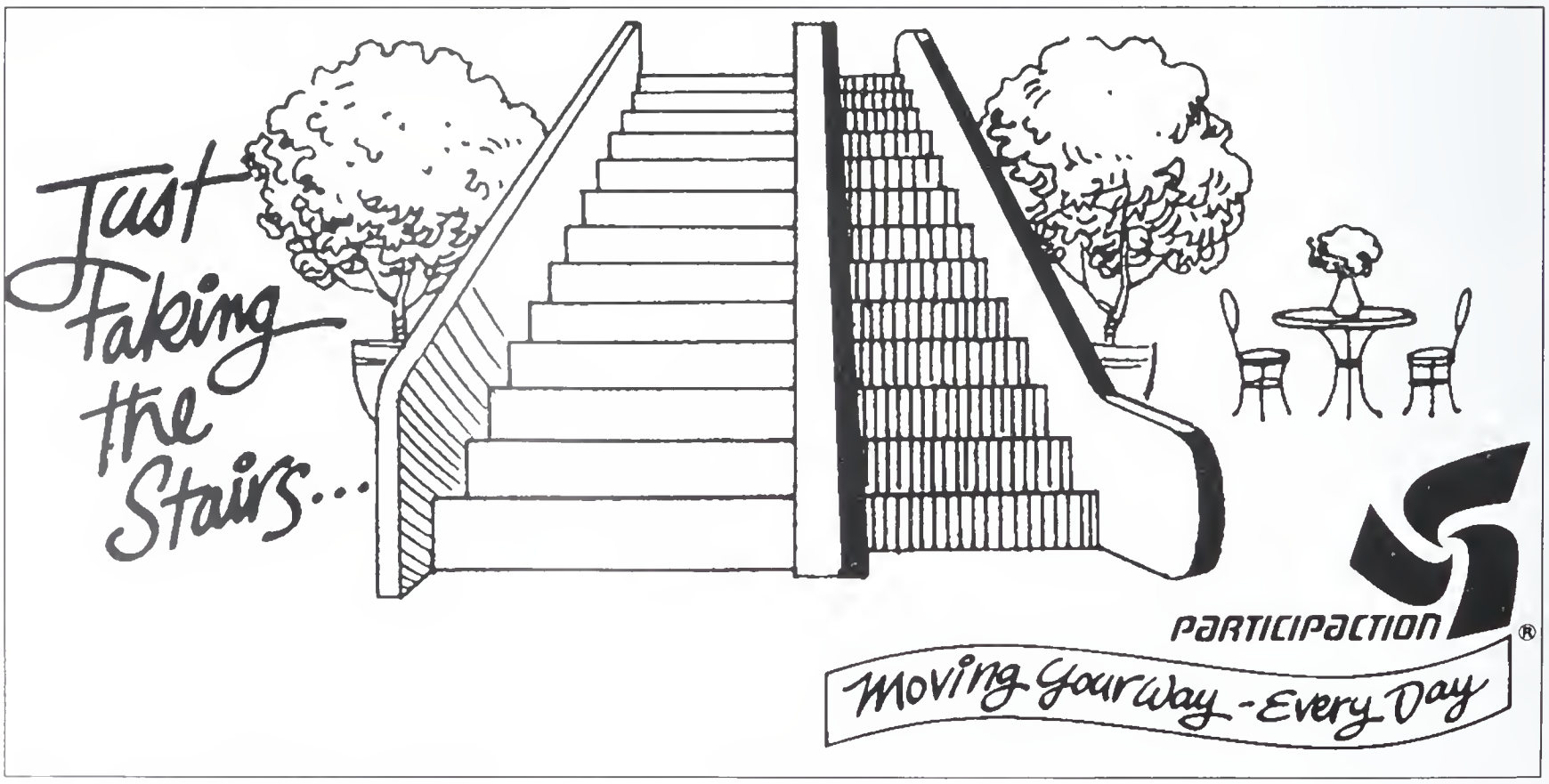

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